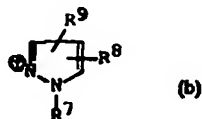
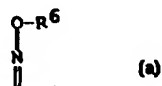
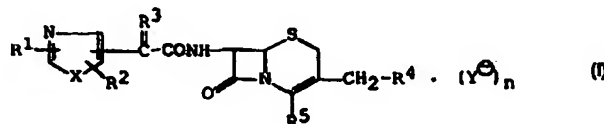




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(54) Title: 3-PYRAZOLIOMETHYLCEPHEM COMPOUNDS AS ANTIMICROBIAL AGENTS



## (S7) Abstract

The present invention relates to a cephem compound of formula (I) wherein R<sup>1</sup> is amino, etc; R<sup>2</sup> is halogen, etc; R<sup>3</sup> is a group of formula (a) (wherein R<sup>6</sup> is hydrogen, etc); R<sup>4</sup> is a group of formula (b) (wherein R<sup>7</sup> is hydroxy(lower)alkyl, etc; R<sup>8</sup> is amino, etc; and R<sup>9</sup> is hydrogen, etc), etc; R<sup>5</sup> is -COO<sup>⊖</sup>, etc; X is -S- etc; Y<sup>⊖</sup> is *m* anion, and *n* is 0 or 1, and a salt thereof, which is useful as a medicament; the processes for the preparation of said cephem compound or a salt thereof; a pharmaceutical composition comprising said cephem compound or a pharmaceutically acceptable salt thereof; etc.

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## DESCRIPTION

## 3-Pyrazolylmethylcephem compounds as antimicrobial agents

## 5 TECHNICAL FIELD

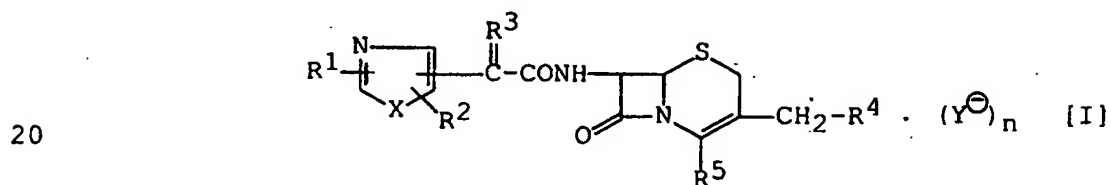
The present invention relates to a new cephem compound and a salt thereof which are useful as a medicament.

## BACKGROUND ART

10 A cephem compound which is more effective against MRSA, etc is needed.

## DISCLOSURE OF INVENTION

15 The object cephem compound of the present invention can be represented by the following formula [I] :



wherein  $R^1$  is amino or a protected amino,  
 $R^2$  is halogen, lower alkyl, cyano or  
 25 lower alkylthio,  
 $R^3$  is a group of the formula :



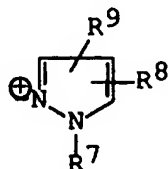
30

[wherein

35

$R^6$  is hydrogen, lower alkyl which may have one or more substituent(s), lower alkenyl which may have one or more substituent(s), lower alkynyl,

cyclo(lower)alkenyl, or acyl],  
 lower alkylidene or oxo,  
 $R^4$  is a group of the formula :



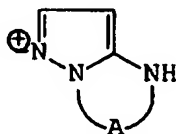
[wherein

$R^7$  is hydroxy(lower)alkyl or protected  
 hydroxy(lower)alkyl,

$R^8$  is amino or a protected amino, and

$R^9$  is hydrogen or lower alkyl],

or a group of the formula :



(wherein A is lower alkylene),

$R^5$  is  $\text{-COO}^\ominus$ , carboxy or a protected carboxy,

X is  $\text{-S-}$  or  $\text{-O-}$ ,

$Y^\ominus$  is an anion, and

n is 0 or 1,

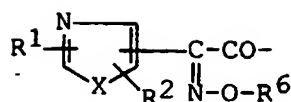
with proviso that

(i) when  $R^5$  is  $\text{-COO}^\ominus$ , then n is 0, and

(ii) when  $R^5$  is carboxy or a protected carboxy, then n is 1.

As to the object compound [I], the following points are  
 to be noted.

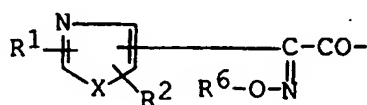
That is, the object compound [I] includes Z isomer, E  
 isomer and a mixture thereof. Z isomer means one geometrical  
 isomer having the partial structure represented by the  
 following formula :



5

(wherein X, R<sup>1</sup>, R<sup>2</sup> and R<sup>6</sup> are each as defined above), and E isomer means the other geometrical isomer having the partial structure represented by the following formula :

10

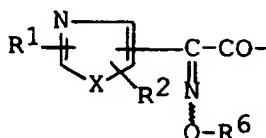


15

(wherein X, R<sup>1</sup>, R<sup>2</sup> and R<sup>6</sup> are each as defined above), and all of such geometrical isomers and mixture thereof are included within the scope of this invention.

In the present specification and claim, the partial structure of these geometrical isomers and mixture thereof are represented for convenient sake by the following formula :

25

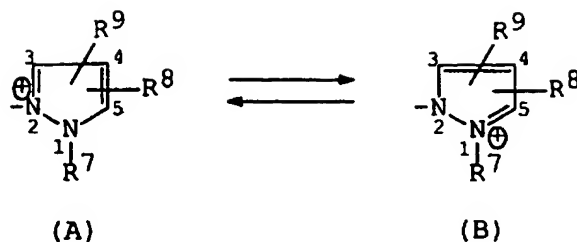


(wherein X, R<sup>1</sup>, R<sup>2</sup> and R<sup>6</sup> are each as defined above).

30

Another point to be noted is that the pyrazolio moiety of the compound [I] can also exist in the tautomeric form, and such tautomeric equilibrium can be represented by the following scheme.

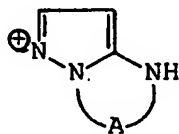
35



(wherein  $R^7$ ,  $R^8$  and  $R^9$  are each as defined above).

10 Both of the above tautomeric isomers are included within the scope of the present invention, and in the present specification and claim, however, the object compound [I] is represented for the convenient sake by one expression of the pyrazolio group of the formula (A).

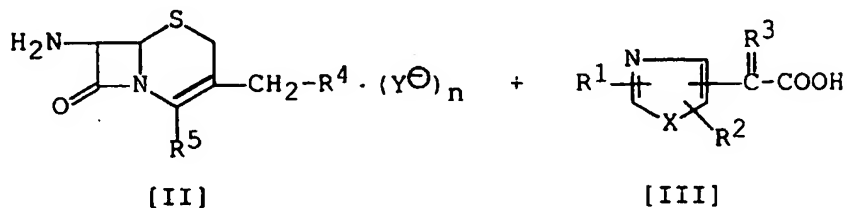
15 As for the group of the formula :



20 (wherein A is as defined above),  
this group can also exist in the similar tautomeric form.

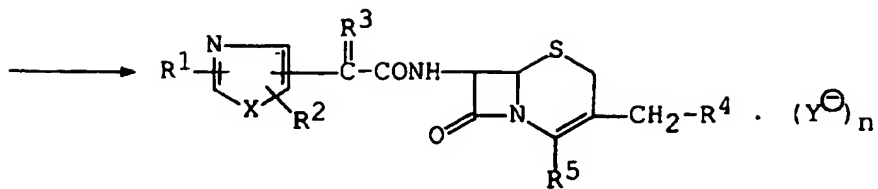
25 The cephem compound [I] of the present invention can be prepared according to the following reaction schemes.

### Process 1



35 or its reactive derivative at the amino group,  
or a salt thereof

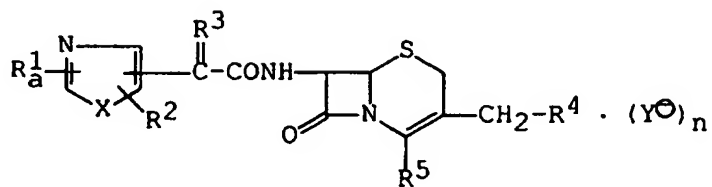
or its reactive derivative at the carboxy group,  
or a salt thereof



[I]

or a salt thereof

10

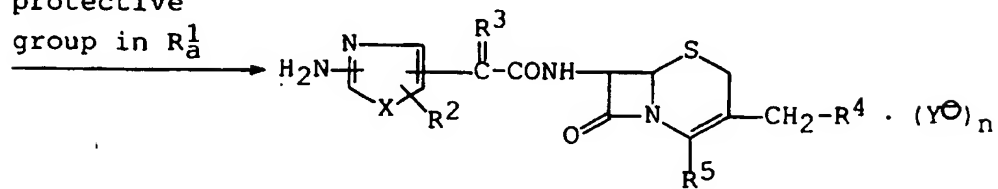
Process 2

[Ia]

or a salt thereof

20

Elimination of  
the amino  
protective  
group in  $\text{R}^1_a$



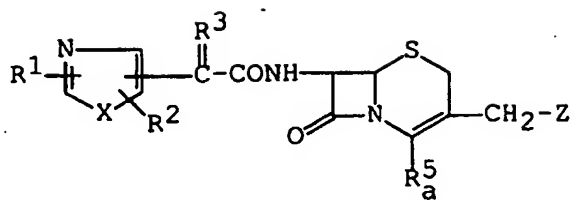
[Ib]

or a salt thereof

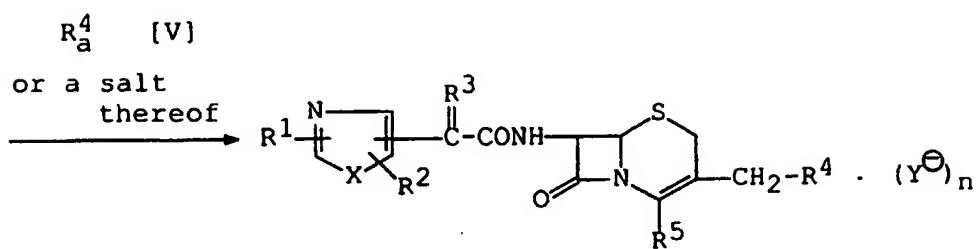
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35

### Process 3

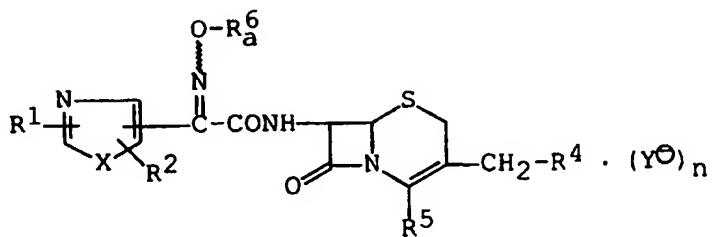


[IV]  
or a salt thereof



[I]  
or a salt thereof

### Process 4

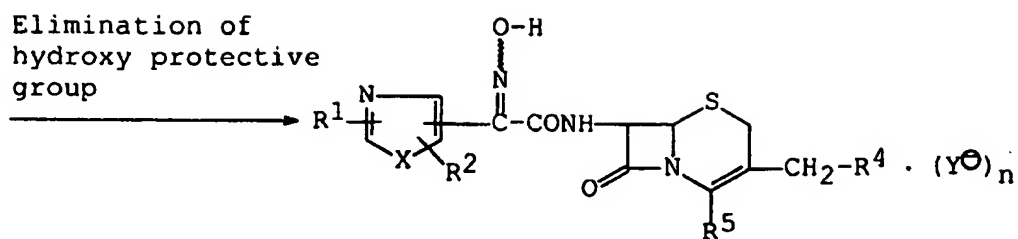


[Ic]  
or a salt thereof



Elimination of  
hydroxy protective  
group

5

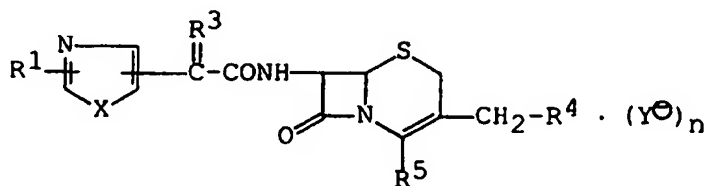


[Id]  
or a salt thereof

10

Process 5

15

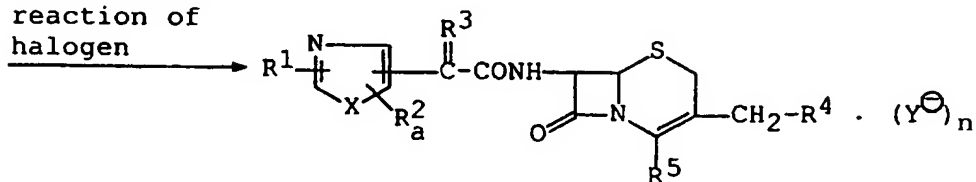


[VI]  
or a salt thereof

20

Introduction  
reaction of  
halogen

25



[Ie]  
or a salt thereof

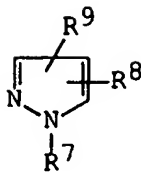
30 wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $X$ ,  $Y^\ominus$  and  $n$  are each as defined  
above,

$R_a^1$  is a protected amino,

$R_a^2$  is halogen,

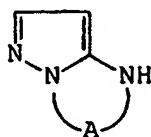
$R_a^4$  is a compound of the formula :

35



(wherein R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are each as defined above)

or a compound of the formula :



(wherein A is as defined above),

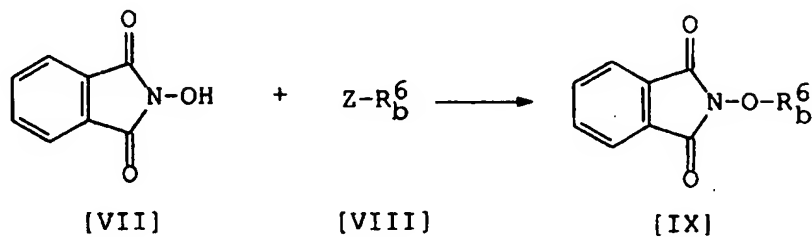
R<sub>a</sub><sup>5</sup> is carboxy or a protected carboxy,

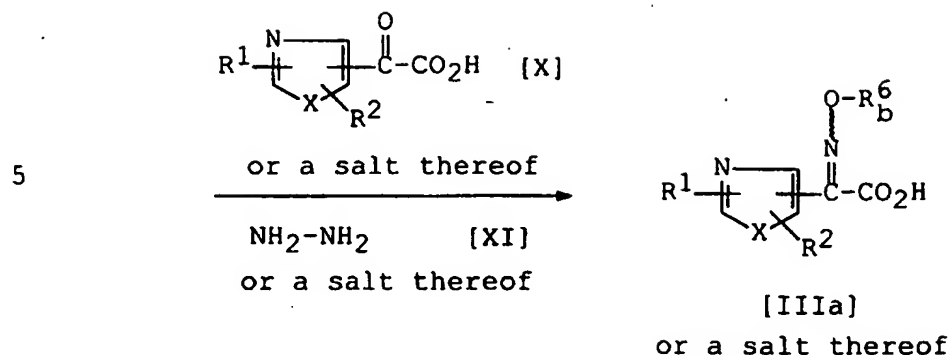
R<sub>a</sub><sup>6</sup> is cyclo(lower)alkenyl or acyl,

Z is a leaving group.

Some of the starting compound [III] can be prepared according to the following reaction schemes.

#### Process A





wherein  $\text{R}^1$ ,  $\text{R}^2$ , X and Z are each as defined above, and  $\text{R}_b^6$  is lower alkyl which may have one or more substituent(s).

15        Suitable salts of the object compound [I] are pharmaceutically acceptable, conventional non-toxic mono or di salts and include a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc],  
 20        an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N-dibenzylethylenediamine salt, etc], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate,  
 25        benzenesulfonate, toluenesulfonate, etc], an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc], a salt with an amino acid [e.g. arginine salt, aspartic acid salt, glutamic acid salt, etc], and the like.

30

In the above and subsequent descriptions of this specification, suitable examples of the various definitions are explained in detail as follows :

35        The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable protective group in "a protected amino" may include ar(lower)alkyl such as mono or di or triphenyl(lower)alkyl [e.g. benzyl, phenethyl, 1-phenylethyl, benzhydryl, trityl, etc], acyl as explained hereinbelow, and  
5 the like.

Suitable "acyl" may be aliphatic acyl, aromatic acyl, arylaliphatic acyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbonic acid, carbamic acid, sulfonic acid, and the like.

10 Suitable example of the acyl group thus explained may be lower alkanoyl [e.g. formyl, acetyl, propionyl, hexanoyl, pivaloyl, etc], mono(or di or tri)halo(lower)alkanoyl [e.g. chloroacetyl, trifluoroacetyl, etc], lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, 15 tert-pentyloxycarbonyl, hexyloxycarbonyl, etc], mono(or di or tri)halo(lower)alkoxycarbonyl [e.g. chloromethoxycarbonyl, dichloroethoxycarbonyl, trichloroethoxycarbonyl, etc], aroyl [e.g. benzoyl, toluoyl, xyloyl, naphthoyl, etc], ar(lower)alkanoyl such as phenyl(lower)alkanoyl [e.g. 20 phenylacetyl, phenylpropionyl, etc], aryloxycarbonyl [e.g. phenoxycarbonyl, naphthyloxycarbonyl, etc], aryloxy(lower)alkanoyl such as phenoxy(lower)alkanoyl [e.g. phenoxyacetyl, phenoxypropionyl, etc], arylglyoxyloyl [e.g. phenylglyoxyloyl, naphthylglyoxyloyl, etc], 25 ar(lower)alkoxycarbonyl which may have suitable substituent(s) such as phenyl(lower)alkoxycarbonyl which may have nitro or lower alkoxy [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, etc], thienylacetyl, 30 imidazolylacetyl, furylacetyl, tetrazolylacetyl, triazolylacetyl, thiadiazolylacetyl, thienylpropionyl, thiadiazolylpropionyl, lower alkylsulfonyl [e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, pentylsulfonyl, butylsulfonyl, etc], 35 arylsulfonyl [e.g. phenylsulfonyl, tolylsulfonyl,

xylylsulfonyl, naphthylsulfonyl, etc], ar(lower)alkylsulfonyl such as phenyl(lower)alkylsulfonyl [e.g. benzylsulfonyl, phenethylsulfonyl, benzhydrylsulfonyl, etc], and the like.

Preferable example of "a protected amino" thus defined may be ar(lower)alkylamino, lower alkanoylamino and lower alkoxycarbonylamino, more preferable one may be triphenyl-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, C<sub>1</sub>-C<sub>4</sub> alkanoylamino and (C<sub>1</sub>-C<sub>4</sub>)-alkoxycarbonylamino, and the most preferable one may be tritylamino, formamido, acetamido and t-butoxycarbonylamino.

Suitable "lower alkyl" may be straight or branched ones such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, 2-ethylpropyl, hexyl or the like, in which the preferred "lower alkyl" may be (C<sub>1</sub>-C<sub>4</sub>)alkyl.

Suitable "lower alkenyl" may be straight or branched ones such as vinyl, allyl, 2-butenyl, 2-methyl-3-butenyl, 3-pentenyl, 1-hexenyl, or the like, in which the preferred one may be (C<sub>2</sub>-C<sub>4</sub>)alkenyl.

Suitable "lower alkynyl" may be straight or branched ones such as ethynyl, 2-propynyl, 3-butynyl, 2-methyl-3-butynyl, 2-pentynyl, 5-hexynyl, or the like, in which the preferred one may be (C<sub>2</sub>-C<sub>4</sub>)alkynyl.

Suitable "halogen" may be fluoro, chloro, bromo, or iodo.

Suitable examples of "substituent(s)" in "lower alkyl" which may have one or more substituent(s)" may include 1 to 3 halogen; cyano; aryl [e.g. phenyl, naphthyl, anthryl, etc]; lower alkylthio; carboxy; protected carboxy; hydroxy(lower)alkyl; protected hydroxy(lower)alkyl; heterocyclic group which may have one or more (preferably 1 to 3) substituent(s) such as lower alkyl, ar(lower)alkyl or the like; heterocyclicthio; and the like.

Suitable "lower alkylthio" may include methylthio, ethylthio, propylthio, butylthio, t-butylthio, pentylthio, hexylthio, and the like, in which the preferred one may be (C<sub>1</sub>-C<sub>4</sub>)alkylthio.

Suitable "protected carboxy" may be

- (1) an esterified carboxy, in which concrete examples of esterified carboxy may be the ones such as lower alkoxy carbonyl (e.g. methoxy carbonyl, ethoxy carbonyl, propoxy carbonyl, isopropoxy carbonyl, butoxy carbonyl, isobutoxy carbonyl, t-butoxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, 1-cyclopropylethoxy carbonyl, etc) which may have suitable substituent(s), for example, lower alkanoyloxy(lower)alkoxy carbonyl [e.g. acetoxymethoxy carbonyl, propionyloxymethoxy carbonyl, butyryloxymethoxy carbonyl, valeryloxymethoxy carbonyl, pivaloyloxymethoxy carbonyl, 1-acetoxyethoxy carbonyl, 1-propionyloxyethoxy carbonyl, pivaloyloxymethoxy carbonyl, 2-propionyloxyethoxy carbonyl, hexanoyloxymethoxy carbonyl, etc]; lower alkanesulfonyl(lower)alkoxy carbonyl [e.g. 2-mesyloxy carbonyl, etc]; mono(or di or tri)halo(lower)alkoxy carbonyl [e.g. 2-iodoethoxy carbonyl, 2,2,2-trichloroethoxy carbonyl, etc]; lower alkenyloxy carbonyl [e.g. vinyloxy carbonyl, allyloxy carbonyl, etc]; lower alkynyloxy carbonyl [e.g. ethynyloxy carbonyl, propynyloxy carbonyl, etc]; ar(lower)alkoxy carbonyl [preferably mono-(or di- or tri-)phenyl(lower)alkoxy carbonyl] which may have suitable substituent(s) [e.g. benzyloxy carbonyl, 4-methoxybenzyloxy carbonyl, 4-nitrobenzyloxy carbonyl, phenethyloxy carbonyl, trityloxy carbonyl, benzhydryloxy carbonyl, bis(methoxyphenyl)methoxy carbonyl, 3,4-dimethoxybenzyloxy carbonyl, 4-hydroxy-3,5-di-t-butylbenzyloxy carbonyl, etc]; aryloxy carbonyl which may have suitable substituent(s) [e.g. phenoxy carbonyl, 4-chlorophenoxy carbonyl, tolyloxy carbonyl, 4-t-butylphenoxy carbonyl, xylyloxy carbonyl, mesityloxy carbonyl, cumenyloxy carbonyl, etc]; or the like;
- (2) amidated carboxy, in which concrete examples of amidated carboxy may be carbamoyl;

N-(lower)alkylcarbamoyl (e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N-isopropylcarbamoyl, N-butylcarbamoyl, N-pentylcarbamoyl, N-hexylcarbamoyl, etc);

5 N-(higher)alkylcarbamoyl (e.g. N-heptylcarbamoyl, N-(2-methylheptyl)carbamoyl, N-nonylcarbamoyl, N-decanylcarbamoyl, N-tricyclo[3.3.1.1<sup>3,7</sup>]decanylcarbamoyl, N-undecanylcarbamoyl, N-(bicyclo[4.3.2]undecanyl)carbamoyl, N-dodecanylcarbamoyl, N-tridecanylcarbamoyl, N-tetradecanylcarbamoyl, N-pentadecanylcarbamoyl, 10 N-hexadecanylcarbamoyl, N-heptadecanylcarbamoyl, N-octadecanylcarbamoyl, N-nonadecanylcarbamoyl, N-icosanylcarbamoyl, etc);

N,N-di(lower)alkylcarbamoyl [e.g. N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, 15 N,N-dipropylcarbamoyl, N,N-di(t-butyl)carbamoyl, N-pentyl-N-hexylcarbamoyl, etc]; and the like, in which the preferred one may be lower alkoxycarbonyl and carbamoyl, and the more preferred one may be (C<sub>1</sub>-C<sub>4</sub>)-alkoxycarbonyl and carbamoyl.

20 Suitable "hydroxy(lower)alkyl" may include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 3-hydroxypropyl, 1-(hydroxymethyl)ethyl, 1-hydroxybutyl, 1-hydroxymethyl-1-methylethyl, 3-hydroxypentyl, 3-hydroxy-2-ethylpropyl, 6-hydroxyhexyl and the like, in which the 25 preferred one may be hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl.

Suitable "protected hydroxy(lower)alkyl" may include acyloxy(lower)alkyl and the like, in which suitable "acyl" moiety can be referred to the ones as exemplified for "a protected amino" before and suitable examples of said 30 "acyloxy(lower)alkyl may be lower alkanoyloxy(lower)alkyl [e.g. formyloxymethyl, 1-formyloxyethyl, 2-formyloxyethyl, 2-acetoxyethyl, 3-acetoxypropyl, 1-(propionyloxymethyl)ethyl, 1-butyryloxybutyl, 1-hexanoyloxybutyl, 1-pivaloyloxymethyl-1-methylethyl, 3-formyloxypentyl, 3-formyloxy-2-ethylpropyl, 35 6-acetoxyhexyl, etc], carbamoyloxy(lower)alkyl [e.g.

carbamoyloxymethyl, 1-carbamoyloxyethyl, 2-carbamoyloxyethyl,  
3-carbamoyloxypropyl, 1-(carbamoyloxymethyl)ethyl,  
1-carbamoyloxybutyl, 1-carbamoyloxymethyl-1-methylethyl,  
3-carbamoyloxypentyl, 3-carbamoyloxy-2-ethylpropyl,  
5 6-carbamoyloxyhexyl, etc] or the like;  
in which the preferred one may be (C<sub>1</sub>-C<sub>4</sub>)alkanoyloxy-  
(C<sub>1</sub>-C<sub>4</sub>)alkyl or carbamoyloxy(C<sub>1</sub>-C<sub>4</sub>)alkyl and the most  
preferred one may be 2-formyloxyethyl, 2-acetoxyethyl or  
2-carbamoyloxyethyl.

10

Suitable "heterocyclic group" and "heterocyclic" moiety  
in the term of "heterocyclicthio" may include saturated or  
unsaturated, monocyclic or polycyclic heterocyclic group  
such as

15

unsaturated 3 to 8-membered (more preferably 5 to 7-  
membered) heteromonocyclic group containing 1 to 4 nitrogen  
atom(s), for example, azepinyl (e.g. 1H-azepinyl, etc),  
pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its  
N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl,  
20 triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl,  
2H-1,2,3-triazolyl, etc), tetrazolyl (e.g. 1H-tetrazolyl,  
2H-tetrazolyl, etc), etc;

25

saturated 3 to 8-membered (more preferably 5 to 7-  
membered) heteromonocyclic group containing 1 to 4 nitrogen  
atom(s), for example, perhydroazepinyl (e.g. perhydro-1H-  
azepinyl, etc), pyrrolidinyl, imidazolidinyl, piperidyl,  
piperazinyl, etc;

30

unsaturated condensed heterocyclic group containing 1 to  
4 nitrogen atom(s), for example, indolyl, isoindolyl,  
indolizinyll, benzimidazolyl, quinolyl, isoquinolyl,  
indazolyl, benzotriazolyl, quinoxalinyl, imidazopyridyl [e.g.  
imidazo[4,5-c]pyridyl, etc], tetrahydroimidazopyridyl [e.g.  
4,5,6,7-tetrahydro[4,5-c]pyridyl, etc], etc;

35

saturated condensed heterocyclic group containing 1 to 4  
nitrogen atom(s), for example, 7-azabicyclo[2.2.1]heptyl,



3-azabicyclo[3.2.2]nonanyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc), etc;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example,

morpholinyl, sydnonyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc), dihydrothiazinyl, etc;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc;

saturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), and

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom

and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc; or the like.

Suitable examples of "substituent(s)" in the term of "heterocyclic group which may have one or more substituent(s)" may include 1 to 3 lower alkyl and ar(lower)alkyl, in which the preferred one may be (C<sub>1</sub>-C<sub>4</sub>)alkyl and triphenyl(C<sub>1</sub>-C<sub>4</sub>)alkyl.

Suitable "lower alkylidene" may include methylene, ethylidene, propylidene, 1-methylethylidene, butylidene, pentylidene, hexylidene, and the like, in which the preferred one may be (C<sub>1</sub>-C<sub>4</sub>)alkylidene.

Suitable "cyclo(lower)alkenyl" may be cyclo(C<sub>3</sub>-C<sub>8</sub>)-alkenyl such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl or the like, in which the preferred one may be cyclo(C<sub>5</sub>-C<sub>7</sub>)alkenyl such as cyclopentenyl, cyclohexenyl or cycloheptenyl.

Suitable examples of "substituent(s)" in lower alkenyl which may have one or more substituent(s)" may include 1 to 3 carboxy, protected carboxy, and the like, in which the preferred one may be carboxy and lower alkoxycarbonyl, the more preferred one may be carboxy and (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl.

Suitable "lower alkylene" may be straight or branched ones such as methylene, ethylene, trimethylene, methylethylene, tetramethylene, pentamethylene, hexamethylene or the like, in which the preferred one may be (C<sub>1</sub>-C<sub>4</sub>)-alkylene.

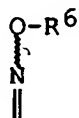
Suitable "an anion" may be formate, acetate,

trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, chloride, bromide, iodide, sulfate, phosphate, or the like.

Suitable "a leaving group" may be halogen [e.g. chlorine, bromine, iodine, etc], acyloxy such as sulfonyloxy [e.g. benzenesulfonyloxy, tosyloxy, mesyloxy, etc], lower alkanoyloxy [e.g. acetyloxy, propionyloxy, etc], or the like.

One of the preferred embodiments of the present invention is the compound [I] wherein  
 $R^1$  is amino, lower alkanoylamino, lower alkoxycarbonylamino or triphenyl(lower)alkylamino,  
 $R^2$  is halogen, lower alkyl, cyano or lower alkylthio,  
 $R^3$  is a group of the formula :

15



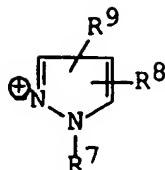
[wherein

$R^6$  is hydrogen; lower alkyl; halo(lower)alkyl; dihalo(lower)alkyl; cyano(lower)alkyl; triphenyl(lower)alkyl; lower alkylthio(lower)alkyl; carboxy(lower)alkyl; lower alkoxycarbonyl(lower)alkyl; carbamoyl(lower)alkyl; hydroxy(lower)alkyl; lower alkanoyloxy(lower)alkyl; pyrazolyl(lower)alkyl or tetrazolyl(lower)alkyl, each of which may have lower alkyl or triphenyl(lower)alkyl; triazolylthio(lower)alkyl; lower alkenyl; carboxy(lower)alkenyl; lower alkoxycarbonyl(lower)alkenyl; lower alkynyl; cyclo(lower)alkenyl; or lower alkanoyl],

lower alkylidene, or oxo,

$R^4$  is a group of the formula :

35



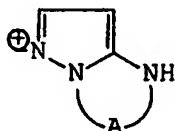
[wherein

$R^7$  is hydroxy(lower)alkyl, lower alkanoyloxy(lower)-alkyl, or carbamoyloxy(lower)alkyl,

$R^8$  is amino or lower alkanoylamino, and

$R^9$  is hydrogen], or

a group of the formula :



(wherein A is lower alkylene), and

$R^5$ , X,  $Y^\ominus$  and n are each as defined above,

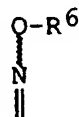
in which the more preferred one may be the compound [I]

wherein

$R^1$  is amino,

$R^2$  is halogen, lower alkyl, cyano or lower alkylthio,

$R^3$  is a group of the formula :



[wherein

$R^6$  is hydrogen; lower alkyl; halo(lower)alkyl;

dihalo(lower)alkyl; cyano(lower)alkyl;

triphenyl(lower)alkyl; lower

alkylthio(lower)alkyl; carboxy(lower)alkyl;

lower alkoxycarbonyl(lower)alkyl;

carbamoyl(lower)alkyl; hydroxy(lower)alkyl;

lower alkanoyloxy(lower)alkyl;

pyrazolyl(lower)alkyl or

tetrazolyl(lower)alkyl, each of which may have  
 lower alkyl or triphenyl(lower)alkyl;  
 triazolylthio(lower)alkyl; lower alkenyl;  
 carboxy(lower)alkenyl; lower  
 5 alkoxy carbonyl(lower)alkenyl; lower alkynyl;  
 cyclo(lower)alkenyl; or lower alkanoyl],

R<sup>4</sup> is a group of the formula :



[wherein

R<sup>7</sup> is hydroxy(lower)alkyl, or

R<sup>8</sup> is amino, and

15 R<sup>9</sup> is hydrogen], or

a group of the formula :



(wherein A is lower alkylene),

R<sup>5</sup> is -COO<sup>⊖</sup>, and

X is -S-.

25 The processes for preparing the object compound of the  
 present invention are explained in detail in the following.

#### Process 1

30 The object compound [I] or a salt thereof can be  
 prepared by reacting a compound [II] or its reactive  
 derivative at the amino group or a salt thereof with a  
 compound [III] or its reactive derivative at the carboxy  
 group or a salt thereof.

35 Suitable reactive derivative at the amino group of the  
 compound [II] may include Schiff's base type imino or its

tautomeric enamine type isomer formed by the reaction of the compound [II] with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound [II] with a silyl compound such as  
5 bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound [II] with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound [II] and its reactive  
10 derivative can be referred to the ones as exemplified for the compound [I].

Suitable reactive derivative at the carboxy group of the compound [III] may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like.  
15 Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc],  
20 dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic  
25 acid, etc] or aromatic carboxylic acid [e.g. benzoic acid, etc]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g. cyanomethyl ester methoxymethyl  
30 ester, dimethyliminomethyl [ $(\text{CH}_3)_2\text{N}^+=\text{CH}-$ ] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl  
35 thioester, pyranyl ester, pyridyl ester, piperidyl ester,

8-quinolyl thioester, etc], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound [III] to be used.

Suitable salts of the compound [III] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylacetamide, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound [III] is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; phosphorus pentachloride; thionyl chloride; mesyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)-

isoxazolium hydroxide intramolecular salt;  
1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole;  
so-called Vilsmeier reagent prepared by the reaction of  
N,N-dimethylformamide with thionyl chloride, phosgene,  
5 trichloromethyl chloroformate, phosphorus oxychloride,  
methanesulfonyl chloride, etc; or the like.

The reaction may also be carried out in the presence of  
an inorganic or organic base such as an alkali metal  
carbonate, alkali metal bicarbonate, tri(lower)alkylamine,  
10 pyridine, N-(lower)alkylmorpholine, N,N-  
di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the  
reaction is usually carried out under cooling to warming.

## 15 Process 2

The object compound [Ib] or a salt thereof can be  
prepared by subjecting a compound [Ia] or a salt thereof to  
elimination reaction of the amino protective group in  $R_a^1$ .

This reaction is carried out in accordance with a  
20 conventional method such as hydrolysis, reduction or the  
like.

The hydrolysis is preferably carried out in the presence  
of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an  
25 organic base such as an alkali metal [e.g. sodium, potassium,  
etc], an alkaline earth metal [e.g. magnesium, calcium, etc],  
the hydroxide or carbonate or bicarbonate thereof,  
trialkylamine [e.g. trimethylamine, triethylamine, etc],  
picoline, 1,5-diazabicyclo[4.3.0]non-5-ene,  
30 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-  
7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic  
acid, acetic acid, propionic acid, trichloroacetic acid,  
trifluoroacetic acid, etc] and an inorganic acid [e.g.  
35 hydrochloric acid, hydrobromic acid, sulfuric acid, etc].



The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc].

5       The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The  
10       reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reaction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

15       Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc] or metallic compound [e.g. chromium chloride, chromium acetate, etc] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid,  
20       p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum,  
25       platinum oxide, platinum wire, etc], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc], nickel  
30       catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc], iron catalysts [e.g. reduced iron, Raney iron, etc], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc] and the like.

The reduction is usually carried out in a conventional  
35       solvent which does not adversely influence the reaction such

as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a  
5 suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc, or a mixture thereof.

10 The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

### Process 3

15 The object compound [I] or a salt thereof can be prepared by reacting a compound [IV] or a salt thereof with a compound [V] or a salt thereof.

Suitable salts of the compounds [IV] can be referred to the ones as exemplified for the compound [I].

20 Suitable salts of the compounds [V] may be an organic acid salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc], an inorganic acid salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc], or the like.

25 The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, methanol, ethanol, diethyl ether, tetrahydrofuran, dimethyl sulfoxide,  
30 or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound [V] is in liquid, it can also be used as a solvent. The reaction is preferably  
35 conducted in the presence of a base, for example, inorganic

base such as alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, organic base such as trialkylamine, and the like. The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating. The present reaction is preferably carried out in the presence of alkali metal halide [e.g. sodium iodide, potassium iodide, etc], alkali metal thiocyanate [e.g. sodium thiocyanate, potassium thiocyanate, etc] or the like.

Anion  $Y^{\ominus}$  may be the one derived from a leaving group Z and may be the other one converted therefrom by a conventional method.

#### Process 4

The object compound [Id] or a salt thereof can be prepared by subjecting a compound [Ic] or a salt thereof to elimination reaction of the hydroxy protective group.

This reaction can be carried out in a similar manner to that of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent, reaction temperature, etc] of this reaction are to be referred to those as explained in Process 2.

#### Process 5

The object compound [Ie] or a salt thereof can be prepared by subjecting a compound [VI] or a salt thereof to introduction reaction of halogen.

This reaction can be carried out by reacting a compound [VI] or a salt thereof with an introduction agent of halogen such as N-halo-succinimide (e.g. N-bromosuccinimide, N-iodosuccinimide, etc), etc.

This reaction can be carried out in a solvent such as N,N-dimethylformamide, N,N-dimethylacetamide or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

The object compound [I] or a salt thereof can be prepared according to the methods other than Processes 1 to 5, and then can be carried out, for examples, as described in Examples.

The reactions in Process A for preparing the starting compound [III] or a salt thereof can be carried out according to the methods as described in Preparations or to the similar manners thereto.

In order to show the utility of the compound [I], the test data on MIC (minimal inhibitory concentration) of representative compound [I] of this invention is shown in the following.

Test Method :

In vitro antibacterial activity was determined by the two-fold agar-plate dilution method as described below.

One loopful of an overnight culture of each test strain in Trypticase-soy broth ( $10^6$  viable cells per ml) was streaked on heart infusion agar (HI-agar) containing graded concentrations of representative test compound, and the minimal inhibitory concentration (MIC) was expressed in terms of  $\mu\text{g/ml}$  after incubation at  $37^\circ\text{C}$  for 20 hours.

Test Compound

(1)  $7\beta$ -[(2)-2-Cyanomethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate  
(the compound of Example 8)

Test Result

MIC ( $\mu\text{g}/\text{ml}$ )

Test Bacteria	Test Compound (1)
S. aureus 3004	6.25

5

For therapeutic administration, the object compound [I] and a pharmaceutically acceptable salt thereof of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active  
10 ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or  
15 liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as  
20 lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound [I] may vary from and  
25 also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compound [I] to be applied, etc. In general, amounts between 1 mg and about 4,000 mg or even more per day may be administered to a patient. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg,  
30 2000 mg of the object compound [I] of the present invention may be used in treating diseases infected by pathogenic microorganisms.

The following Preparations and Examples are given for  
35 the purpose of illustrating some preferred embodiments of the

present invention in more detail.

#### Preparation 1

A solution of bromoacetonitrile (8.82 g) in 67 ml of  
5 N,N-dimethylformamide was treated portionwise with  
N-hydroxyphthalimide (10.0 g) and powdered potassium  
carbonate (16.9 g) at 0°C. The mixture was allowed to stir  
at room temperature. The reaction mixture was poured into  
670 ml of water to afford 8.03 g of  
10 N-(cyanomethoxy)phthalimide as precipitates.

IR (KBr) :  $1740\text{ cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 7.92 (4H, s), 5.25 (2H, s)

#### Preparation 2

15 A solution of N-hydroxyphthalimide (3.38 g) and 1-bromo-  
2,2-difluoroethane (3.0 g) in 8 ml of N,N-dimethylformamide  
was treated with triethylamine (6.2 ml) at 0°C. The mixture  
was allowed to warm to 80°C. After 24 hours, additional 1-  
bromo-2,2-difluoroethane (1.5 g) in 4 ml of N,N-  
20 dimethylformamide was introduced. The reaction mixture was  
quenched by water and extracted with ethyl acetate. The  
combined extracts were washed with water, aqueous sodium  
hydrogen carbonate and brine, and were dried with magnesium  
sulfate. The solvent was removed under reduced pressure and  
25 the residue was washed with isopropyl ether to afford 3.50 g  
of N-(2,2-difluoroethoxy)phthalimide.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 7.89 (4H, s), 6.34 (1H, tt,  $J=54\text{Hz}$ ,  
3.8Hz), 4.50 (1H, dd,  $J=14.2\text{Hz}$ , 3.8Hz), 4.43 (1H,  
dd,  $J=14.2\text{Hz}$ , 3.8Hz)

30 MS (APCI)  $m/z$  : 228 ( $M^+ + 1$ )

#### Preparation 3

To a solution of N-(2-fluoroethoxy)phthalimide (9.3 g)  
in tetrahydrofuran (180 ml) was added dropwise hydrazine  
35 monohydrate (2.9 ml) under ice-cooling with stirring and the

mixture was stirred for 1.5 hours at 25 to 35°C. The insoluble material was filtered off, and the filtrate was adjusted to pH 7.0 with aqueous sodium hydrogen carbonate. To the neutral solution was added 2-(2-formylamino-5-chlorothiazol-4-yl)-2-oxoacetic acid (10.5 g), and the mixture was stirred at room temperature for 3 hours with keeping the pH value between 4.5-5.0 with saturated aqueous sodium hydrogen carbonate. The reaction mixture was poured into ethyl acetate (300 ml), and adjusted to pH 3.0 with 1N-hydrochloric acid. The separated organic phase was washed with water (200 ml) and dried with magnesium sulfate and evaporated in vacuo to give (Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-(2-fluoroethoxyimino)acetic acid (9.6 g).

NMR (DMSO- $d_6$ ,  $\delta$ ) : 4.25-4.35 (1H, m), 4.45-4.55 (1H, m), 4.50-4.60 (1H, m), 4.75-4.85 (1H, m), 8.55 (1H, s), 12.89 (1H, br s)

#### Preparation 4

A solution of N-(2,2-difluoroethoxy)phthalimide (1.94 g) in 39 ml of methanol and 14 ml of dichloromethane was treated with hydrazine monohydrate (0.64 g) at 0°C. The insoluble material was filtered off and 2-oxo-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid (2.0 g) was added to the filtrate at room temperature. After 3 hours, the insoluble material was filtered off and the solvent was removed under reduced pressure. Ethyl acetate was added and the insoluble material was filtered off again, and the filtrate was removed under reduced pressure, and the residue was washed with isopropyl ether to afford 2.44 g of (Z)-2-(2,2-difluoroethoxyimino)-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid.

IR (KBr) : 3169, 1720, 1659, 1068, 1045  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 8.55 (1H, s), 7.84 (1H, s), 6.26 (1H, tt,  $J=54.6\text{Hz}$ ,  $3.7\text{Hz}$ ), 4.45 (1H, dd,  $J=14.5\text{Hz}$ ,

3.7Hz), 4.37 (1H, dd, J=14.5Hz, 3.7Hz)

#### Preparation 5

(Z)-2-Cyanomethoxyimino-2-(5-chloro-2-formylaminothiazol-4-yl)acetic acid (12.61 g) was obtained according to a similar manner to that of Preparation 4.

NMR (DMSO-d<sub>6</sub>, δ) : 12.93 (1H, s), 8.57 (1H, s),  
5.16 (2H, s)

#### Example 1

A mixture of N,N-dimethylformamide (0.67 ml) and phosphorus oxychloride (0.8 ml) in tetrahydrofuran (20 ml) was stirring for 30 minutes at 5°C, (Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-allyloxyiminoacetic acid (2.09 g) was added thereto with stirring and ice-cooling, and the mixture was stirred for 30 minutes at 5°C to produce an activated acid solution. On the other hand, 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (2.3 g) was dissolved in a solution of mono-trimethylsilylacetamide (8 g) in N,N-dimethylformamide (23 ml) and tetrahydrofuran (23 ml). To the solution was at a time added the above obtained activated acid solution at 5°C and the mixture was stirred for 1.5 hours at 5°C. The resulting solution was poured into ethyl acetate (1 l). The resulting powder was collected by filtration, and dried in vacuo to give 7β-[(Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-allyloxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (4.4 g).

NMR (DMSO-d<sub>6</sub>, δ) : 3.2-3.40 (2H, m), 3.50-3.65 (2H, m),  
4.05-4.55 (2H, m), 4.50-4.65 (2H, m), 5.05-5.40  
(2H+2H, m), 5.15 (1H, d, J=4.9Hz), 5.80-6.05  
(1H+1H+1H, m), 7.96 (2H, br s), 8.07 (1H, d,  
J=3.2Hz), 8.53 (1H, s), 9.74 (1H, d, J=8.4Hz), 12.9  
(1H, s)



Example 2

A mixture of N,N-dimethylformamide (2.8 ml) and phosphorus oxychloride (3.4 ml) in tetrahydrofuran (90 ml) was stirred for 30 minutes at 5°C. (Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(2-fluoroethoxyimino)acetic acid (9 g) was added thereto with stirring and ice-cooling, and the mixture was stirred for 30 minutes at 5°C to produce an activated acid solution. On the other hand, 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (12.7 g) was dissolved in a solution of mono-trimethylsilylacetamide (44.4 g) in N,N-dimethylformamide (120 ml) and tetrahydrofuran (120 ml). To the solution was at a time added the above obtained activated acid solution at 5°C, and the mixture was stirred for 1.5 hours at 5°C. The resulting solution was poured into ethyl acetate (3 l). The precipitate was collected by filtration and dried under reduced pressure. The powder was dissolved in water (300 ml), adjusted to pH 4.0 with aqueous sodium hydrogen carbonate and then subjected to column chromatography on HP-20 (Trademark : Mitsubishi Kasei Corporation) (500 ml), and eluted with 20% 2-propanol and the eluate was lyophilized to give 7β-[(Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-(2-fluoroethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (5.8 g).

IR (KBr) : 1774, 1673, 1608, 1542, 1284, 1068 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 2.96 and 3.24 (2H, ABq, J=17.1Hz), 3.40-3.60 (2H, m), 4.05-4.40 (2H+1H), 4.40-4.50 (1H, m), 4.50-4.60 (1H, m), 4.70-4.80 (1H, m), 5.04 (1H, d, J=4.9Hz), 5.07 and 5.23 (2H, ABq, J=18.0Hz), 5.68 (1H, dd, J=4.9Hz, 8.4Hz), 5.84 (1H, d, J=3.1Hz), 7.39 (2H, br s), 8.09 (1H, d, J=3.1Hz), 8.54 (1H, s), 9.68 (1H, d, J=8.4Hz)

35 Example 3

To a solution of (Z)-2-(2,2-difluoroethoxyimino)-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid (1.67 g) in 16 ml of N,N-dimethylacetamide, powdered potassium carbonate (0.74 g) and methanesulfonyl chloride (1.22 g) were added  
5 stepwise at 0°C. On the other hand, a suspension of 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (2.0 g) in 20 ml of N,N-dimethylacetamide was treated portionwise with N-(trimethylsilyl)acetamide (4.19 g) at room temperature. Both  
10 reaction mixture were combined at 0°C and stirred for 3 hours. The reaction was quenched by dropping into 300 ml of ethyl acetate to get precipitates, which were purified by column chromatography on HP-20 resin to get 0.71 g of  
15 7β-[(Z)-2-(2,2-difluoroethoxyimino)-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 1772, 1676, 1650, 1610 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 9.71 (1H, d, J=8.4Hz), 8.53 (1H, s),  
8.11 (1H, d, J=2.9Hz), 7.32 (2H, br s), 6.24 (1H,  
20 br t, J=54.6Hz), 5.82 (1H, d, J=2.9Hz), 5.65 (1H, dd, J=8.4Hz, 4.7Hz), 5.22, 5.06 (2H, ABq, J=14.9Hz), 5.03 (1H, d, J=4.7Hz), 4.2-4.6 (2H, m), 4.37 (2H, br t, J=14.6Hz), 3.5-3.7 (2H, m), 3.21, 2.94 (2H, ABq, J=16.9Hz)

25 MS (FAB) m/z : 635.1 (M<sup>+</sup>), 637.1 (M<sup>+</sup>+2)

#### Example 4

7β-[(Z)-2-Cyanomethoxyimino-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (3.24 g) was obtained  
30 according to a similar manner to that of Example 3.

MS (FAB) m/z : 610.3 (M<sup>+</sup>)

#### Example 5

35 To a suspension of 7β-[(Z)-2-(2-formylamino-5-

chlorothiazol-4-yl)-2-allyloxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (3.74 g) in methanol (37 ml) was added concentrated hydrochloric acid (2.9 ml) under stirring at 25°C to 30°C.

5 The stirring was continued for 3 hours at 20°C to 30°C. The reaction mixture was poured into a cooled water (100 ml) and adjusted to pH 4.0 with saturated aqueous sodium hydrogen carbonate. To the resulting solution was evaporated in vacuo. The residue was subjected to column chromatography on  
10 HP-20 (200 ml), and eluted with 15% 2-propanol and the eluate was lyophilized to give 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-allyloxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (520 mg).

15 IR (KBr) : 1776, 1666, 1585, 1539, 1388, 1352, 1016 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 2.91 and 3.17 (2H, ABq, J=17Hz),  
3.40-3.65 (2H, m), 4.20-4.60 (2H, m), 4.50-4.60  
(2H, m), 4.99 (1H, d, J=5Hz), 5.05-5.50 (2H+2H, m),  
5.61 (1H, dd, J=5Hz, 8Hz), 5.81 (1H, d, J=3Hz),  
20 5.85-6.05 (1H, m), 7.27 (2H, br s), 7.41 (2H, br s), 8.10 (1H, d, J=3Hz), 9.54 (1H, d, J=8Hz)

#### Example 6

25 7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-(2-fluoroethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (2.75 g) was obtained according to a similar manner to that of Example 5.

IR (KBr) : 1772, 1612, 1538, 1392, 1355, 1064 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>, δ) : 2.94 and 3.21 (2H, ABq, J=17.2Hz),  
30 3.40-3.65 (2H, m), 4.15-4.25 (1H, m), 4.25-4.50 (1H+1H, m), 4.55-4.65 (1H, m), 4.70-4.85 (1H, m), 5.01 (1H, d, J=4.8Hz), 5.04 (2H, ABq, J=18.2Hz), 5.62 (1H, dd, J=4.8Hz, 7.9Hz), 5.82 (1H, d, J=2.9Hz), 7.34 (2H, br s), 7.39 (2H, br s), 8.09  
35 (1H, d, J=2.9Hz), 9.54 (1H, d, J=7.9Hz)

Example 7

A solution of 7 $\beta$ -[(Z)-2-(2,2-difluoroethoxyimino)-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.71 g) in 3.6 ml of methanol was treated with hydrochloric acid (0.47 ml), and stirred for 4 hours at room temperature. The reaction mixture was dropped into 300 ml of ethyl acetate to get precipitates, which were purified by column chromatography on HP-20 resin to get 0.40 g of 7 $\beta$ -[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(2,2-difluoroethoxyimino)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 1770, 1649, 1616  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 9.60 (1H, d, J=8.4Hz), 8.11 (1H, d, J=3.1Hz), 7.44 (2H, br s), 7.30 (2H, br s), 6.20 (1H, tt, J=54.9Hz, 3.7Hz), 5.82 (1H, d, J=3.1Hz), 5.61 (1H, dd, J=8.4Hz, 4.9Hz), 5.22, 5.05 (2H, ABq, J=15.1Hz), 5.00 (1H, d, J=4.9Hz), 4.2-4.6 (2H, m), 4.31 (2H, dt, J=3.7Hz, 14.1Hz), 3.5-3.7 (2H, m), 3.20, 2.93 (2H, ABq, J=17.6Hz)

MS (FAB) m/z : 606.9 ( $\text{M}^+$ ), 609.1 ( $\text{M}^++2$ )

Example 8

7 $\beta$ -[(Z)-2-Cyanomethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]-methyl-3-cephem-4-carboxylate (92 mg) was obtained according to a similar manner to that of Example 7.

IR (KBr) : 1770, 1666, 1614  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 9.72 (1H, d, J=8.4Hz), 8.11 (1H, d, J=3.2Hz), 7.49 (2H, br s), 7.28 (2H, br s), 5.81 (1H, d, J=3.2Hz), 5.59 (1H, dd, J=8.4Hz, 4.9Hz), 5.19, 5.07 (2H, ABq, J=15Hz), 5.01 (1H, d, J=4.9Hz), 5.00 (2H, s), 4.2-4.6 (2H, m), 3.2-3.8 (2H, m), 2.88, 3.21 (2H, ABq, J=17.1Hz)

MS (FAB) m/z : 582.0 ( $\text{M}^+$ ), 584.1 ( $\text{M}^++2$ )

Preparation 6

A solution of ethyl 2-hydroxyimino-3-oxopentanoate (20 g) in 140 ml of ethyl acetate was treated with diethyl sulfate (19.59 g) and powdered potassium carbonate (18.36 g). The reaction mixture was quenched by water and extracted with ethyl acetate. The combined extracts were washed with water and brine, and were dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 19:1) to afford 11.11 g of ethyl 2-ethoxyimino-3-oxopentanoate.

IR (Neat) : 1747, 1695  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.00 (3H, t,  $J=7.3\text{Hz}$ ), 1.23 (3H, t,  $J=7.1\text{Hz}$ ), 1.27 (3H, t,  $J=7.1\text{Hz}$ ), 2.81 (2H, q,  $J=7.3\text{Hz}$ ), 4.27 (2H, q,  $J=7.1\text{Hz}$ ), 4.32 (2H, q,  $J=7.1\text{Hz}$ )

Preparation 7

A solution of ethyl 2-ethoxyimino-3-oxopentanoate (11.11 g) in 11 ml of acetic acid was treated dropwise with sulfuric chloride (5.06 ml). The mixture was stirred for 3 hours at 50°C and quenched by ice-water. The mixture was extracted with ethyl acetate, and the combined extracts were washed with brine and dried with magnesium sulfate. The solvent was removed under reduced pressure to afford 14.15 g of ethyl 4-chloro-2-ethoxyimino-3-oxopentanoate.

IR (Neat) : 1747, 1705  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.25 (3H, t,  $J=7.1\text{Hz}$ ), 1.29 (3H, t,  $J=7.0\text{Hz}$ ), 1.59 (3H, d,  $J=6.7\text{Hz}$ ), 4.31 (2H, q,  $J=7.1\text{Hz}$ ), 4.38 (1H, q,  $J=7.0\text{Hz}$ ), 5.33 (1H, q,  $J=6.7\text{Hz}$ )

Preparation 8

A solution of ethyl 4-chloro-2-ethoxyimino-3-

oxopentanoate (14.15 g) in 44 ml of water and 44 ml of ethanol was treated portionwise with thiourea (6.86 g) and sodium acetate (7.39 g) at room temperature. The mixture was allowed to stir at 40°C. The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the precipitates were filtered and washed with water and dried under reduced pressure to afford 10.17 g of ethyl (Z)-2-ethoxyimino-2-(2-amino-5-methylthiazol-4-yl)acetate.

IR (KBr) : 3138, 1724, 1630, 1545  $\text{cm}^{-1}$   
NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.21 (3H, t,  $J=7.0\text{Hz}$ ), 1.24 (3H, t,  $J=7.1\text{Hz}$ ), 2.36 (3H, s), 4.12 (2H, q,  $J=7.0\text{Hz}$ ), 4.23 (2H, q,  $J=7.1\text{Hz}$ ), 6.95 (2H, s)

#### 15 Preparation 9

A solution of ethyl (Z)-2-ethoxyimino-2-(2-amino-5-methylthiazol-4-yl)acetate (10.0 g) in 50 ml of tetrahydrofuran was treated with 19.4 ml of 4N sodium hydroxide solution. The reaction mixture was allowed to 50°C, and then diluted with water and washed with ethyl acetate. Aqueous phase was allowed to pH 2.5 to afford 7.60 g of (Z)-2-ethoxyimino-2-(2-amino-5-methylthiazol-4-yl)acetic acid as precipitates.

IR (KBr) : 1628  $\text{cm}^{-1}$   
NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.22 (3H, t,  $J=7.0\text{Hz}$ ), 2.36 (3H, s), 4.10 (2H, q,  $J=7.0\text{Hz}$ ), 6.94 (2H, s),

#### Preparation 10

A solution of ethyl (Z)-2-methoxyimino-2-(2-formylaminothiazol-4-yl)acetate (5.0 g) in 50 ml of methanol was treated with N-bromosuccinimide (3.81 g). The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were dried with sodium sulfate. The solvent was removed under reduced pressure to afford 6.8 g of ethyl (Z)-2-methoxyimino-2-(5-bromo-2-

formylaminothiazol-4-yl)acetate.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.28 (3H, t, J=7.1Hz), 3.96 (3H, s),  
4.31 (2H, q, J=7.1Hz), 8.55 (1H, s), 12.84 (1H, s)

MS (APCI) m/z : 336 (M<sup>+</sup>)

5

#### Preparation 11

A solution of ethyl (Z)-2-methoxyimino-2-(5-bromo-2-formylaminothiazol-4-yl)acetate (6.8 g) in 68 ml of N,N-dimethylformamide was treated with copper(I) cyanide (2.17 g). The reaction mixture was allowed to 100°C. The reaction was quenched with ice-water, and extracted with ethyl acetate. The solvent was removed under reduced pressure to afford 1.60 g of ethyl (Z)-2-methoxyimino-2-(5-cyano-2-formylaminothiazol-4-yl)acetate.

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IR (KBr) : 2222, 1743, 1691, 1531 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.30 (3H, t, J=6.7Hz), 4.04 (3H, s),  
4.35 (2H, q, J=6.7Hz), 8.70 (1H, s), 13.36 (1H, s),

MS (APCI) m/z : 283 (M<sup>+</sup>+1)

20

#### Preparation 12

A solution of ethyl (Z)-2-methoxyimino-2-(5-cyano-2-formylaminothiazol-4-yl)acetate (0.8 g) in 3.2 ml of dioxane and 3.2 ml of water was treated with sodium hydroxide (0.57 g). After 3 hours, the reaction mixture was diluted with water and washed with ethyl acetate. Aqueous phase was allowed to pH 2 and extracted with ethyl acetate and tetrahydrofuran. The solvent was removed under reduced pressure to afford 0.59 g of (Z)-2-methoxyimino-2-(5-cyano-2-formylaminothiazol-4-yl)acetic acid.

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IR (KBr) : 2218, 1741 cm<sup>-1</sup>

MS (FAB) m/z : 255.0 (M<sup>+</sup>)

#### Preparation 13

A solution of ethyl 2-(2-formylaminothiazol-4-yl)-2-oxoacetate (50 g) in 280 ml of N,N-dimethylformamide was

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treated with a solution of trichloroisocyanuric acid (20.2 g) in 70 ml of N,N-dimethylformamide at 60°C. The reaction mixture was poured into 3.5 l of ice-water to afford 54.15 g of ethyl 2-(5-chloro-2-formylaminothiazol-4-yl)-2-oxoacetate as precipitates.

IR (KBr) : 1749, 1676, 1543, 1086  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.32 (3H, t,  $J=7.1\text{Hz}$ ), 4.38 (2H, q,  $J=7.1\text{Hz}$ ), 8.60 (1H, s), 12.8 (1H, br s)

#### 10 Preparation 14

Ethyl 2-(5-chloro-2-formylaminothiazol-4-yl)-2-oxoacetate (20 g) was added to 45 ml of 4N potassium hydroxide solution. The reaction mixture was diluted with water and washed with ethyl acetate. The aqueous phase was allowed to pH 2, and precipitates were filtered and washed with isopropyl ether to get 15.59 g of 2-(5-chloro-2-formylaminothiazol-4-yl)-2-oxoacetic acid.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 8.59 (1H, s), 13.56 (1H, br s)

#### 20 Preparation 15

A solution of (Z)-2-difluoromethoxyimino-2-(2-tritylaminothiazol-4-yl)acetic acid (20 g) in 300 ml of methanol was treated with N-chlorosuccinimide (6.13 g) and stirred at 70°C. After 7 hours, additional N-chlorosuccinimide (1.67 g) was introduced. The reaction mixture was diluted with water and allowed to pH 7, and washed with ethyl acetate. The aqueous phase was allowed to pH 2.6, and was extracted with ethyl acetate. The combined extracts were dried with sodium sulfate. The solvent was removed under reduced pressure to afford 8.88 g of (Z)-2-difluoromethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetic acid.

IR (KBr) : 3305, 3201, 1707, 1645  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 7.20 (1H, t,  $J=70.8\text{Hz}$ ),  
7.60 (2H, br s)



MS (APCI) m/z : 272 ( $M^+ + 1$ )

#### Preparation 16

5 N-(Fluoromethoxy)phthalimide was prepared according to a similar manner to that of Preparation 1.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 5.78 (2H, d,  $J=53.0\text{Hz}$ ), 7.91 (4H, s)

MS (APCI) m/z : 195 ( $M^+$ )

#### Preparation 17

10 (Z)-2-Fluoromethoxyimino-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid was obtained according to a similar manner to that of Preparation 3.

IR (KBr) : 1739, 1720, 1685  $\text{cm}^{-1}$

15 NMR (DMSO- $d_6$ ,  $\delta$ ) : 5.82 (2H, d,  $J=55.1\text{Hz}$ ), 8.57 (1H, s), 12.94 (1H, br s)

MS (APCI) m/z : 281.7 ( $M^+$ )

#### Preparation 18

20 A solution of ethyl 2-hydroxyimino-3-oxopentanoate (8.0 g) in 56 ml of ethyl acetate was treated with dimethyl sulfate (6.41 g) and powdered potassium carbonate (7.34 g). The reaction mixture was quenched by water and extracted with ethyl acetate. The combined extracts were washed with water and brine, and were dried with magnesium sulfate. The  
25 solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 19:1) to afford 6.73 g of ethyl 2-methoxyimino-3-oxopentanoate.

IR (Neat) : 1747, 1697  $\text{cm}^{-1}$

30 NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.00 (3H, t,  $J=7.3\text{Hz}$ ), 1.24 (3H, t,  $J=7.1\text{Hz}$ ), 2.81 (2H, q,  $J=7.3\text{Hz}$ ), 4.06 (3H, s), 4.27 (2H, q,  $J=7.1\text{Hz}$ )

#### Preparation 19

35 Ethyl 4-chloro-2-methoxyimino-3-oxopentanoate was

obtained according to a similar manner to that of Preparation 7.

IR (Neat) : 1743, 1701, 1039  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 1.25 (3H, t,  $J=7.1\text{Hz}$ ), 1.59 (3H, d,  $J=6.7\text{Hz}$ ), 4.12 (3H, s), 4.31 (2H, q,  $J=7.1\text{Hz}$ ), 5.31 (1H, q,  $J=6.7\text{Hz}$ )

MS (APCI)  $m/z$  : 222 ( $M^++1$ )

#### Preparation 20

Ethyl (Z)-2-methoxyimino-2-(2-amino-5-methylthiazol-4-yl)acetate was obtained according to a similar manner to that of Preparation 8.

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 1.24 (3H, t,  $J=7.1\text{Hz}$ ), 2.36 (3H, s), 3.87 (3H, s), 4.23 (2H, q,  $J=7.1\text{Hz}$ ) 6.94 (2H, br s),

MS (APCI)  $m/z$  : 244 ( $M^++1$ )

#### Preparation 21

(Z)-2-Methoxyimino-2-(2-amino-5-methylthiazol-4-yl)acetic acid was obtained according to a similar manner to that of Preparation 9.

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 2.36 (3H, s), 3.85 (3H, s), 6.96 (2H, br s)

MS (APCI)  $m/z$  : 216 ( $M^++1$ )

#### Preparation 22

N-(Carbamoylmethoxy)phthalimide was obtained according to a similar manner to that of Preparation 1.

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 4.60 (2H, s), 7.63 (2H, br s), 7.89 (4H, s)

#### Preparation 23

(Z)-2-Carbamoylmethoxyimino-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid was obtained according to a similar manner to that of Preparation 3.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 4.55 (2H, s), 7.09 (1H, br s), 7.46  
(1H, br s), 8.56 (1H, s), 12.92 (1H, s)  
MS (APCI) m/z : 306.9 ( $M^+$ )

5     Preparation 24

(Z)-2-(1-tert-Butoxycarbonyl-1-methylethoxyimino)-2-(2-amino-5-chlorothiazol-4-yl)acetic acid was obtained according to a similar manner to that of Preparation 15.

IR (KBr) : 1732, 1720, 1645, 1146  $\text{cm}^{-1}$

10     NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.39 (9H, s), 1.42 (6H, s),  
7.43 (2H, br s)

MS (APCI) m/z : 364.2 ( $M^+ + 1$ )

Preparation 25

15     To a solution of N-(cyanomethoxy)phthalimide (10.0 g) in tetrahydrofuran (100 ml) was added sodium azide (9.65 g) and aluminum chloride (7.26 g) at 0°C. The reaction mixture was refluxed with stirring. The reaction was quenched by 2N hydrochloric acid. The aqueous phase was extracted with  
20     ethyl acetate, and the combined extracts were washed with brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was washed with isopropyl ether to afford 6.33 g of N-(2H-tetrazol-5-ylmethoxy)phthalimide.

25     NMR (DMSO- $d_6$ ,  $\delta$ ) : 5.50 (2H, s), 7.8-8.0 (4H, m)  
MS (APCI) m/z : 246 ( $M^+ + 1$ )

Preparation 26

30     To a solution of N-(2H-tetrazol-5-ylmethoxy)phthalimide (2.32 g) in dimethylformamide (20 ml) was added trityl chloride (2.90 g) and triethylamine (1.6 ml) at 0°C. After 4 hours, the reaction was quenched by water and extracted with ethyl acetate. The combined extracts were washed with brine and dried with magnesium sulfate. The solvent was removed  
35     under reduced pressure, and the residue was washed with

hexane-ethyl acetate to afford 2.62 g of the mixture of N-(1-trityl-1H-tetrazol-5-ylmethoxy)phthalimide and N-(2-trityl-2H-tetrazol-5-ylmethoxy)phthalimide.

5 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 5.48 (2H, s), 6.9-7.0 (6H, m),  
7.2-7.5 (9H, m), 7.8-7.9 (4H, m)

#### Preparation 27

10 A mixture of 2-[(Z)-(1-trityl-1H-tetrazol-5-ylmethoxyimino))-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid and 2-[(Z)-(2-trityl-2H-tetrazol-5-ylmethoxyimino))-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid were obtained according to a similar manner to that of Preparation 3.

IR (KBr) : 3427, 1732, 1691, 1547 cm<sup>-1</sup>

15 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 5.49 (2H, s), 7.0-7.1 (6H, m),  
7.2-7.4 (9H, m), 8.54 (1H, s), 12.88 (1H, s)

#### Preparation 28

20 A mixture of ethyl chlorofluoroacetate (100 g), phthaloyl chloride (102.5 ml) and chlorosulfonic acid (47.3 ml) was heated at total reflux in a still connected to an ice-cooled receiver backed up by a dry ice cooled trap when the pot temperature reached 120°C, distillation was started and the volatile material was distilled from the reaction mixture until the pot temperature rose to 200°C. The  
25 condensates in the receiver and the dry ice cooled trap were combined. On the other hand, isopropylidene malonate (51.3 g) was dissolved in a solution of pyridine (69.7 ml) in dichloromethane (160 ml). To the solution was added dropwise above obtained combined solution at 5°C to 10°C and the  
30 mixture was stirred for 3 hours at the same temperature. The resulting solution was poured into a cooled 3N-hydrochloric acid (200 ml). The separated organic phase was washed with brine (200 ml), and dried with magnesium sulfate and  
35 evaporated in vacuo. The residue was added methanol (300 ml) at room temperature with stirring. The mixture was refluxed

for 8 hours. The reaction mixture was evaporated in vacuo. The residue was subjected to a column chromatography on silica gel (500 g) and eluted with a mixture of ethyl acetate and hexane (1:2). The fractions containing the objective compound were collected, evaporated to give methyl 4-chloro-4-fluoro-3-oxobutyrate (43.2 g).

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.72 (3H, s), 3.88 (2H, d,  $J=1.6\text{Hz}$ ),  
6.99 (1H, d,  $J=49\text{Hz}$ )

#### 10 Preparation 29

To a solution of methyl 4-chloro-4-fluoro-3-oxobutyrate (31 g) and isopentyl nitrite (25.8 ml) in dichloromethane (120 ml) was added dropwise acetyl chloride (13 ml) under ice-cooling with stirring and the mixture was stirred for 3 hours at 5°C to 10°C. The resulting solution was poured into water (300 ml) and adjusted to pH 3.0 with saturated aqueous sodium hydrogencarbonate. The separated organic phase was washed with water (300 ml) and dried with magnesium sulfate and evaporated in vacuo to give methyl 4-chloro-4-fluoro-2-hydroxyimino-3-oxobutyrate (44.5 g).

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.82 (3H, s), 7.39 (1H, d,  $J=49\text{Hz}$ ),  
14.14 (1H, s)

#### Preparation 30

25 To a solution of methyl 4-chloro-4-fluoro-2-hydroxyimino-3-oxobutyrate (7.8 g) in N,N-dimethylacetamide (80 ml) was added thiourea (15 g) under stirring at 30°C and then the stirring was continued for 12 hours at the same temperature. The resulting solution was poured into a mixture of ethyl acetate (300 ml) and water (400 ml), and adjusted to pH 3.0 with saturated aqueous sodium hydrogencarbonate. The separated organic phase was washed with water (400 ml) and brine (400 ml), and dried with magnesium sulfate and evaporated in vacuo to give methyl (Z)-2-(2-amino-5-fluorothiazol-4-yl)-2-hydroxyiminoacetate (2.17 g).

NMR (DMSO-d<sub>6</sub>, δ) : 3.76 (3H, s), 7.11 (2H, br s),  
11.92 (1H, s)

#### Preparation 31

5 To a suspension of methyl (Z)-2-(2-amino-5-fluorothiazol-4-yl)-2-hydroxyiminoacetate (1 g) in dichloromethane (20 ml) was added dropwise borontrichloride 1M solution in dichloromethane (22.8 ml) under ice-cooling with stirring and the mixture was stirred for 3 hours at 5°C  
10 to 10°C. The resulting solution was poured into a mixture of tetrahydrofuran (30 ml) and brine (15 ml), and adjusted to pH 3.0 with saturated aqueous sodium hydrogencarbonate. The separated organic phase was dried with magnesium sulfate and evaporated in vacuo. The residue was subjected to a column  
15 chromatography on silica gel and eluted with a mixture of ethyl acetate and methanol (2:1). The fractions containing the object compound were combined and evaporated in vacuo to give (Z)-2-(2-amino-5-fluorothiazol-4-yl)-2-hydroxyimino-acetic acid (330.26 mg).

20 NMR (DMSO-d<sub>6</sub>, δ) : 6.94 (2H, br s)  
MS : 206 (M<sup>+</sup>)

#### Preparation 32

A mixture of acetic anhydride (2.7 ml) and formic acid  
25 (2.2 ml) was stirred for 30 minutes at 30°C. (Z)-2-(2-Amino-5-fluorothiazol-4-yl)-2-hydroxyiminoacetic acid (1.2 g) was added thereto with stirring under ice-cooling, and the mixture was stirred for 3 hours at 25°C to 35°C. The reaction mixture was poured into an isopropyl ether (50 ml).  
30 The precipitate was collected by filtration, dried under reduced pressure to give (Z)-2-(2-formylamino-5-fluorothiazol-4-yl)-2-formyloxyiminoacetic acid.

NMR (DMSO-d<sub>6</sub>, δ) : 8.23 (1H, s), 8.50 (1H, s)

#### 35 Preparation 33

Methyl 4-chloro-4-fluoro-2-ethoxyimino-3-oxobutyrates were obtained according to a similar manner to that of Preparation 6.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.37 (3H, t,  $J=7\text{Hz}$ ), 3.85 (3H, s),  
4.05 (2H, m), 7.38 (1H, d,  $J=49\text{Hz}$ )

#### Preparation 34

Methyl (Z)-2-(2-amino-5-fluorothiazol-4-yl)-2-ethoxyiminoacetate was obtained according to a similar manner to that of Preparation 8.

IR (KBr) : 1743, 1631, 1538, 1438, 1299, 1078  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.19 (3H, t,  $J=7\text{Hz}$ ), 3.78 (3H, s),  
4.13 (2H, q,  $J=7\text{Hz}$ ), 7.20 (2H, br s)

#### Preparation 35

(Z)-2-(2-Amino-5-fluorothiazol-4-yl)-2-ethoxyiminoacetic acid was obtained according to a similar manner to that of Preparation 31.

IR (KBr) : 1637, 1604, 1533, 1407, 1359, 1216, 1041  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.76 (3H, t,  $J=7\text{Hz}$ ),  
3.60 (2H, q,  $J=7\text{Hz}$ )

#### Preparation 36

To a suspension of (Z)-2-(2-tritylaminothiazol-4-yl)-2-(2-fluoroethoxyimino)acetic acid in methanol (50 ml), was added N-bromosuccinimide (2.8 g) at room temperature with stirring and the mixture was stirred for 3 hours at 25°C to 35°C. The resulting solution was poured into a mixture of ethyl acetate (250 ml) and water (300 ml), and adjusted to pH 3.0 with aqueous sodium hydrogen carbonate. The separated organic phase was washed with water (200 ml) and dried with magnesium sulfate and evaporated in vacuo to give (Z)-2-(2-amino-5-bromothiazol-4-yl)-2-(2-fluoroethoxyimino)acetic acid (2.64 g).

NMR (DMSO- $d_6$ ,  $\delta$ ) : 4.10-4.15 (1H, m), 4.18-4.23 (1H, m),

4.55-4.60 (1H, m), 4.75-4.80 (1H, m), 7.45 (2H, br s)

### Preparation 37

5 (Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(2-acetoxyethoxyimino)acetic acid was obtained according to a similar manner to that of Preparation 3.

NMR (DMSO-d<sub>6</sub>, δ) : 2.00 (3H, s), 4.05-4.30 (4H, m),  
8.52 (1H, s)

### 10 Preparation 38

(Z)-2-(2-Formylaminothiazol-4-yl)-2-(methylthiomethoxyimino)acetic acid (10 g) was suspended into methanol (100 ml), N-bromosuccinimide (9.7 g) was added thereto at room temperature with stirring and the mixture was stirred for 3  
15 hours at 20°C to 30°C. The resulting solution was poured into a mixture of ethyl acetate (300 ml) and water (300 ml), and adjusted to pH 3.0 with aqueous sodium hydrogencarbonate. The separated organic phase was washed with water (200 ml) and dried with magnesium sulfate and evaporated in vacuo.  
20 The residue was suspended into methanol (100 ml), thereto was added concentrated hydrochloric acid (17.2 ml) at room temperature. After the reaction mixture was stirred at room temperature for 4 hours, it was poured into a mixture of ethyl acetate (400 ml) and water (300 ml). The mixture was  
25 adjusted to pH 3.0 with aqueous sodium hydrogen carbonate. The separated organic phase was washed with water (300 ml) and dried with magnesium sulfate and evaporated in vacuo, to give (Z)-2-(2-amino-5-bromothiazol-4-yl)-2-(methylthio-  
methoxyimino)acetic acid (5.5 g).

30 IR (KBr) : 1704, 1639, 1538, 1376, 1297, 1180, 983 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 2.21 (3H, s), 5.34 (2H, s),  
7.49 (2H, br s)

### Preparation 39

35 To a solution of bromochloromethane (26.4 ml) and



N,N-dimethylformamide (160 ml) was added portionwise  
4-mercapto-1H-1,2,3-triazole sodium salt (20 g) at -20°C, then  
it was stirred under ice-cooling for 20 minutes, at room  
temperature for one hour. The reaction mixture was poured  
5 into ethyl acetate (500 ml) and water (700 ml), it was  
adjusted to pH 7. The organic layer was separated, dried  
over magnesium sulfate, and evaporated. The residue was  
dissolved in N,N-dimethylformamide (250 ml) and pyridine  
(12.6 g), and triphenylmethylchloride (44.6 g) was added to  
10 the solution under ice-cooling. After the reaction mixture  
was stirred at room temperature for 2 hours, it was poured  
into ethyl acetate (750 ml) and water (900 ml), adjusted to  
pH 3.5. The organic layer was separated, dried over  
magnesium sulfate, and concentrated. The resulting  
15 precipitate was collected by filtration, and the precipitate  
was washed with diisopropyl ether. 5-Chloromethylthio-1-  
trityl-1H-1,2,3-triazole (38.2 g) was obtained.

NMR (DMSO-d<sub>6</sub>, δ) : 5.25 (2H, s), 7.00-7.10 (6H, m),  
7.35-7.43 (9H, m), 8.03 (1H, s)

20

#### Preparation 40

To a suspension of 5-chloromethylthio-1-trityl-  
1H-1,2,3-triazole (10.97 g) in acetone (150 ml) was added  
sodium iodide (8.4 g) at room temperature, and then it was  
25 stirred at 50°C for 3 hours. After it was poured into ethyl  
acetate (300 ml) and water (300 ml), the organic layer was  
separated, dried over magnesium sulfate, and evaporated. 60%  
sodium hydride (1.10 g) was added to a solution of  
N-hydroxyphthalimide (4.49 g) in N,N-dimethylformamide (45  
30 ml) at room temperature, it was stirred at the same  
temperature for 30 minutes. The above residue was added  
thereto, the reaction mixture was stirred at 50°C for one  
hour. After it was poured into ethyl acetate (250 ml) and  
water (300 ml), the organic layer was separated, dried over  
35 magnesium sulfate, and evaporated. To the residue

diisopropyl ether (15 ml) was added, the resulting precipitate was collected by filtration. N-(1-trityl-1H-1,2,3-triazol-5-yl)thiomethoxyphthalimide (5.6 g) was obtained.

5           NMR (DMSO- $d_6$ ,  $\delta$ ) : 5.62 (2H, s), 6.95-7.02 (6H, m),  
              7.38-7.45 (9H, m), 7.80 (4H, s), 8.04 (1H, s)  
              MS (FAB) m/z : 519 ( $M^+$ +1)

#### Preparation 41

10           (Z)-2-(2-Formylamino-5-bromothiazol-4-yl)-2-(1-trityl-1H-1,2,3-triazol-5-yl)thiomethoxyiminoacetic acid was obtained according to a similar manner to that of Preparation 3.

15           NMR (DMSO- $d_6$ ,  $\delta$ ) : 5.62 (2H, s), 6.98-7.04 (6H, m),  
              7.30-7.40 (9H, m), 7.85 (1H, s), 8.56 (1H, s)  
              MS (FAB) m/z : 650 ( $M^+$ +1)

#### Preparation 42

20           Methanesulfonyl chloride (15.4 g) was added to an ice-cooling solution of 4-hydroxymethyl-1-methylpyrazole (10 g) and triethylamine (19.8 g) in dichloromethane (100 ml), and the mixture was stirred at 5-10°C for two hours. After it was poured into ice-water (150 ml), organic layer was separated, dried over magnesium sulfate, and evaporated. On the other hand, N-hydroxyphthalimide (12.5 g) and triethylamine (8.57 g) was dissolved in N,N-dimethylformamide (160 ml), thereto was added the above residue at room temperature. The reaction mixture was warmed at 60°C, and it was stirred at the same temperature for 2 hours. The solution was poured into ethyl acetate (500 ml) and water (500 ml), and then the organic layer was separated, dried over magnesium sulfate, and evaporated. N-(1-Methylpyrazol-4-yl)methoxyphthalimide (11.3 g) was obtained.

35           NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.81 (3H, s), 5.04 (2H, s),  
              7.50 (1H, s), 7.85 (5H, s)

MS m/z : 258 ( $M^+ + 1$ )

Preparation 43

(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(1-methylpyrazol-4-yl)methoxyiminoacetic acid (1.15 g) was obtained according to a similar manner to that of Preparation 3.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.82 (3H, s), 5.03 (2H, s), 7.47 (1H, s), 7.75 (1H, s), 8.54 (1H, s), 12.8 (1H, s)

MS (FAB) m/z : 344 ( $M^+ + 1$ )

Preparation 44

To a solution of 4-hydroxymethylpyrazole (5.0 g) in tetrahydrofuran (50 ml) was added di-tert-butyl dicarbonate (11.1 g) and 4-dimethylaminopyridine (20 mg). It was warmed at 50°C for 2 hours. The reaction mixture was concentrated, and subjected to column chromatography (70 g). It was eluted with ethyl acetate. The active fractions were collected, concentrated to give 1-tert-butoxycarbonyl-4-hydroxymethylpyrazole (7.9 g)

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.57 (9H, s), 4.38 (2H, d,  $J=5.4\text{Hz}$ ), 5.04 (1H, t,  $J=5.4\text{Hz}$ ), 7.73 (1H, s), 8.08 (1H, s)

MS m/z : 199 ( $M^+ + 1$ )

Preparation 45

N-(1-tert-Butoxycarbonylpyrazol-4-yl)methoxyphthalimide was obtained according to a similar manner to that of Preparation 42.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.57 (9H, s), 5.12 (2H, s), 7.86 (4H, s), 7.92 (1H, s), 8.43 (1H, s)

MS m/z : 344 ( $M^+ + 1$ )

Preparation 46

(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(1-tert-butoxycarbonylpyrazol-4-yl)methoxyiminoacetic acid was

obtained according to a similar manner to that of Preparation 3.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.58 (9H, s), 5.13 (2H, s), 7.85 (1H, s), 8.33 (1H, s), 8.54 (1H, s)

5 MS (FAB) m/z : 429 ( $M^+$ )

#### Preparation 47

(Z)-2-(2-Formylaminothiazol-4-yl)-2-(3-cyclopentenyl)-oxyiminoacetic acid (15.0 g) was suspended into methanol (150 ml), and N-bromosuccinimide (10.5 g) was added thereto with ice-cooling. After the reaction mixture was stirred at room temperature for 2 hours, it was concentrated to 70 ml. The solution was poured into ethyl acetate (300 ml) and water (300 ml), and then it was adjusted to pH 3.0 with sodium hydrogen carbonate. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated. (Z)-2-(2-Formylamino-5-bromothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetic acid (8.1 g) was obtained.

IR (KBr) : 3159, 3080, 2800, 1774, 1697, 1639, 1192  $cm^{-1}$

20 NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.80-2.50 (4H, m), 5.29 (1H, m), 5.90 (1H, m), 6.13 (1H, m), 8.05 (1H, m)

MS (FAB) m/z : 360 ( $M^+$ )

#### Preparation 48

25 (Z)-2-(2-Aminothiazol-4-yl)-2-ethoxyiminoacetic acid (7.0 g) was suspended into methanol (105 ml), and N-iodosuccinimide (8.1 g) was added thereto with ice-cooling. After the reaction mixture was stirred at room temperature for an hour, ethyl acetate (100 ml) was added thereto, and the resulting precipitate was collected by filtration. (Z)-2-(2-Amino-5-iodothiazol-4-yl)-2-ethoxyiminoacetic acid (3.8 g) was obtained.

IR (KBr) : 1709, 1645, 1599, 1041  $cm^{-1}$

35 NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.28 (3H, t,  $J=7.0Hz$ ), 4.14 (2H, q,  $J=7.0Hz$ ), 7.43 (2H, s), 11.07 (1H, s)

The following compounds (Preparations 49 and 50) were obtained according to a similar manner to that of Preparation 48.

5     Preparation 49

(Z)-2-(2-Amino-5-bromothiazol-4-yl)-2-ethoxyiminoacetic acid

IR (KBr) : 1705, 1643, 1595, 1568  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.24 (3H, t,  $J=7.0\text{Hz}$ ), 4.14 (2H, q,  $J=7.0\text{Hz}$ ), 7.86 (2H, br)

10

MS (FAB)  $m/z$  : 294 ( $M^+$ ), 296 ( $M^++2$ )

Preparation 50

(Z)-2-(2-Amino-5-iodothiazol-4-yl)-2-acetoxyminoacetic acid

15

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.24 (3H, s), 7.55 (2H, s)

Preparation 51

(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(1-tritylimidazol-4-yl)methoxyiminoacetic acid was obtained according to a similar manner to that of Preparation 3

20

NMR (DMSO- $d_6$ ,  $\delta$ ) : 5.05 (2H, s), 6.95 (1H, s), 7.25-7.40 (16H, m), 8.54 (1H, s), 12.86 (1H, br s)

25

Preparation 52

Methyl (Z)-2-(2-tert-butoxycarbonylamino-5-chlorothiazol-4-yl)-2-pentenoate was obtained according to a similar manner to that of Preparation 13.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.10 (3H, t,  $J=7.5\text{Hz}$ ), 1.52 (9H, s),

30

2.47 (2H, qin,  $J=7.5\text{Hz}$ ), 3.78 (3H, s), 6.56 (1H, t,  $J=7.5\text{Hz}$ )

Preparation 53

To a solution of methyl (Z)-2-(2-tert-butoxycarbonylamino-5-chlorothiazol-4-yl)-2-pentenoate (3 g)

35

in 2-propanol (9 ml) was added 1N-sodium hydroxide solution (27 ml) under at 30°C. The stirring was continued for 3 hours at the same temperature. The reaction mixture was poured into a mixture of ethyl acetate (200 ml) and water (50 ml). The separated organic phase was washed with brine (100 ml) and dried over magnesium sulfate and evaporated in vacuo to give (Z)-2-(2-tert-butoxycarbonylamino-5-chlorothiazol-4-yl)-2-pentenoic acid (1.7 g).

NMR (DMSO-d<sub>6</sub>, δ) : 1.07 (3H, t, J=7.5Hz), 1.47 (9H, s),  
2.44 (2H, qin, J=7.5Hz), 6.38 (1H, t, J=7.5Hz)

#### Preparation 54

Ethyl (Z)-2-(2-tert-butoxycarbonylamino-5-chlorooxazol-4-yl)-2-ethoxyiminoacetate was obtained according to a similar manner to that of Preparation 13.

NMR (DMSO-d<sub>6</sub>, δ) : 1.15-1.35 (6H, m), 1.42 (9H, s),  
4.23 (2H, q, J=7.0Hz), 4.32 (2H, q, J=7.1Hz)

#### Preparation 55

To a solution of ethyl (Z)-2-(2-tert-butoxycarbonylamino-5-chlorooxazol-4-yl)-2-ethoxyiminoacetate (1.85 g) in dichloromethane (5.6 ml) and anisole (1.85 ml) was added dropwise trifluoroacetic acid (3.7 ml) at 20°C. The stirring was continued for 2 hours at 30°C. The reaction mixture was poured into isopropyl ether (100 ml). The resulting powder was collected by filtration, and dried in vacuo to give ethyl (Z)-2-(2-amino-5-chlorooxazol-4-yl)-2-ethoxyiminoacetate (930 mg).

NMR (DMSO-d<sub>6</sub>, δ) : 1.05-1.35 (6H, m), 4.10-4.4 (4H, m),  
7.25 (2H, br s)

MS (APCI) m/z : 262 (M+H)<sup>+</sup>

#### Preparation 56

(Z)-2-(2-Amino-5-chlorooxazol-4-yl)-2-ethoxyiminoacetic acid was obtained according to a similar manner to that of

Preparation 31.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.10-1.40 (6H, m), 4.00-4.40 (4H, m), 7.02 (2H, br s)

MS (APCI) m/z : 234 (M+H)<sup>+</sup>

5

The following compounds (Examples 9 to 21) were obtained according to a similar manner to that of Example 3.

Example 9

10 7 $\beta$ -[(Z)-2-(2-Amino-5-fluorothiazol-4-yl)-2-ethoxyimino-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1614, 1535, 1353, 1220, 1062 cm<sup>-1</sup>

15 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.20 (3H, t, J=7Hz), 2.93 and 3.19 (2H, ABq, J=17Hz), 3.50-3.70 (2H, m), 4.07 (2H, q, J=7Hz), 4.15-4.55 (2H, m), 5.00 (1H, d, J=5Hz), 5.05 and 5.22 (2H, ABq, J=18Hz), 5.60 (1H, dd, J=5Hz, 8Hz), 5.81 (1H, d, J=3Hz), 7.12 (2H, br s), 7.28 (2H, br s), 8.10 (1H, d, J=3Hz), 9.50 (1H, d, J=8Hz)

20

MS (FAB) m/z : 555 (M<sup>+</sup>)

Example 10

25 7 $\beta$ -[(Z)-2-(2-Amino-5-bromothiazol-4-yl)-2-(2-fluoroethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1666, 1639, 1614, 1535, 1392 cm<sup>-1</sup>

30 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.89 and 3.20 (2H, ABq, J=17Hz), 3.40-3.65 (2H, m), 4.05-4.55 (2H+2H, m), 4.55-4.95 (2H, m), 5.00 (1H, d, J=5Hz), 5.05 and 5.21 (2H, ABq, J=18Hz), 5.60 (1H, dd, J=5Hz, 8Hz), 5.81 (1H, d, J=3Hz), 7.27 (2H, br s), 7.42 (2H, br s), 8.10 (1H, d, J=3Hz), 9.52 (1H, d, J=8Hz)

35

Example 11

7 $\beta$ -[(Z)-2-(2-Amino-5-bromothiazol-4-yl)-2-(methylthiomethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1612, 1537, 1351, 1218, 1064 cm<sup>-1</sup>

5 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.21 (3H, s), 2.90 and 3.17 (2H, ABq, J=17Hz), 3.40-3.65 (2H, m), 4.23-4.60 (2H, m), 5.00 (1H, d, J=5Hz), 5.05-5.25 (2H+2H, m), 5.69 (1H, dd, J=5Hz, 8Hz), 5.81 (1H, d, J=3Hz), 7.28 (2H, br s), 7.45 (2H, br s), 8.10 (1H, d, J=3Hz),  
10 9.56 (1H, d, J=8Hz)

#### Example 12

7 $\beta$ -[(Z)-2-(2-tert-Butoxycarbonylamino-5-chlorothiazol-4-yl)-2-pentenoylamino]-3-[1-(2-hydroxyethyl)-5-amino-2-pyrazolio]methyl-3-cephem-4-carboxylate

15 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.01 (3H, t, J=7.5Hz), 1.46 (9H, s), 2.10-2.30 (2H, m), 3.10-3.30 (2H, m), 3.30-3.70 (2H, m), 4.00-4.45 (2H, m), 5.10-5.40 (3H, m), 5.80-5.95 (2H, m), 6.37 (1H, t, J=7.5Hz), 7.32 (2H, br s), 8.08 (1H, d, J=3.1Hz), 9.30 (1H, d, J=8.0Hz)  
20

#### Example 13

7 $\beta$ -[(Z)-2-(2-Amino-5-chlorooxazol-4-yl)-2-ethoxyiminoacetamido]-3-[1-(2-hydroxyethyl)-5-amino-2-pyrazolio]-methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1668, 1602, 1585, 1392, 1043 cm<sup>-1</sup>

30 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.21 (3H, t, J=7.0Hz), 3.00 and 3.23 (2H, ABq, J=17.3Hz), 3.35-3.80 (2H, m), 4.06 (2H, q, J=7.0Hz), 4.20-4.55 (2H, m), 5.06 (1H, d, J=5.0Hz), 5.0-5.45 (2H, m), 5.66 (1H, dd, J=8.4Hz, 5.0Hz), 5.83 (1H, d, J=3.1Hz), 7.15 (2H, br s), 7.28 (2H, br s), 8.08 (1H, d, J=3.1Hz), 9.57 (1H, d, J=8.4Hz)

#### 35 Example 14



7 $\beta$ -[(Z)-2-tert-Butoxycarbonylmethoxyimino-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

MS (FAB) m/z : 684.9 (M<sup>+</sup>)

5

Example 15

7 $\beta$ -[(Z)-2-Carbamoylmethoxyimino-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

10 MS (FAB) m/z : 628.2 (M<sup>+</sup>), 630.2 (M<sup>+</sup>+2)

Example 16

7 $\beta$ -[(Z)-2-(1-tert-Butoxycarbonyl-1-methylethoxyimino)-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

15

IR (KBr) : 1788, 1643 cm<sup>-1</sup>

MS (FAB) m/z : 685.1 (M<sup>+</sup>), 687.2 (M<sup>+</sup>+2)

Example 17

20 7 $\beta$ -[(Z)-2-(3-tert-Butoxycarbonylallyloxyimino)-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1749, 1684, 1649, 1541 cm<sup>-1</sup>

MS (FAB) m/z : 711.0 (M<sup>+</sup>), 713.2 (M<sup>+</sup>+2)

25

Example 18

7 $\beta$ -[(Z)-2-Ethoxyimino-2-(2-amino-5-methylthiazol-4-yl)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

30

IR (KBr) : 3336, 1772, 1649, 1610 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.22 (3H, t, J=7.0Hz), 2.33 (3H, s),  
3.18, 2.91 (2H, ABq, J=17.0Hz), 3.5-3.7 (2H, m),  
4.07 (2H, q, J=7.0Hz), 4.2-4.6 (2H, m), 4.99 (1H,  
d, J=4.8Hz), 5.21, 5.04 (2H, ABq, J=15Hz), 5.59  
35 (1H, dd, J=8.6Hz, 4.8Hz), 5.81 (1H, d, J=3.1Hz),

6.90 (2H, br s), 7.27 (2H, br s), 8.10 (1H, d, J=3.1Hz), 9.34 (1H, d, J=8.6Hz)

MS (FAB) m/z : 551.0 ( $M^+ + 1$ )

5     Example 19

7 $\beta$ -[(Z)-2-Trityloxyimino-2-(2-tritylamino-5-methylthiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1792, 1774  $\text{cm}^{-1}$

10     MS (FAB) m/z : 1007.3 ( $M^+$ )

Example 20

7 $\beta$ -[(Z)-2-Methoxyimino-2-(2-amino-5-methylthiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1649, 1614, 1045  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.33 (3H, s), 2.91, 3.19 (ABq, 2H, J=17.4Hz), 3.5-3.7 (2H, m), 3.81 (3H, s), 4.2-4.6 (2H, m), 4.99 (1H, d, J=4.8Hz), 5.04, 5.21 (2H, ABq, J=15.3Hz), 5.59 (1H, dd, J=8.6Hz, 4.8Hz), 5.82 (1H, d, J=3.2Hz), 6.91 (2H, br s), 7.33 (2H, br s), 8.10 (1H, d, J=3.2Hz), 9.37 (1H, d, J=8.6Hz)

MS (FAB) m/z : 537.2 ( $M^+ + 1$ )

25     Example 21

7 $\beta$ -[(Z)-2-Methoxyimino-2-(2-formylamino-5-cyanothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

MS (FAB) m/z : 576.1 ( $M^+ + 1$ )

30

Example 22

To a solution of phosphorus pentachloride (2.3 g) in 40 ml of dichloromethane, (Z)-2-difluoromethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetic acid (2.0 g) was added at -30°C and stirred at -15°C for 2 hours to generate acid chloride in

35

situ. A solution of 7 $\beta$ -amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (2.77 g) and N-(trimethylsilyl)acetamide (9.66 g) in 28 ml of N,N-dimethylformamide and 28 ml of tetrahydrofuran was added to the acid chloride solution at 0°C. After 3 hours, the reaction mixture was dropped into 600 ml of ethyl acetate to get precipitates, which were purified by column chromatography on HP-20 resin and preparative HPLC to get 57 mg of 7 $\beta$ -[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 1774, 1668, 1639, 1614 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.91, 3.20 (2H, ABq, J=17.3Hz), 3.4-3.9 (2H, m), 4.2-4.6 (2H, m), 5.03 (1H, d, J=4.9Hz), 5.06, 5.21 (2H, ABq, J=15.1Hz), 5.61 (1H, dd, J=8.2Hz, 4.9Hz), 5.81 (1H, d, J=3.1Hz), 7.12 (1H, t, J=70.8Hz), 7.28 (2H, br s), 7.54 (2H, br s), 8.10 (1H, d, J=3.1Hz), 9.87 (1H, d, J=8.2Hz),

MS (FAB) m/z : 593.0 (M<sup>+</sup>)

#### Example 23

7 $\beta$ -[(Z)-2-(5-Chloro-2-formylaminothiazol-4-yl)-2-(fluoromethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate was obtained according to a similar manner to that of Example 22.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.94, 3.25 (2H, ABq, J=17.4Hz), 3.5-3.8 (2H, m), 4.2-4.6 (2H, m), 5.06 (1H, d, J=4.8Hz), 5.08, 5.21 (2H, ABq, J=15.4Hz), 5.67 (1H, dd, J=8.4Hz, 4.8Hz), 5.77 (2H, d, J=53.7Hz), 5.83 (1H, d, J=3.1Hz), 7.31 (2H, br s), 8.09 (1H, d, J=3.1Hz), 8.55 (1H, s), 9.81 (1H, d, J=8.4Hz)

MS (FAB) m/z : 603.0 (M<sup>+</sup>)

#### Example 24

Phosphorus pentachloride (2.48 g) was suspended into dichloromethane (19 ml), and then it was cooled to  $-20^{\circ}\text{C}$ , and (Z)-2-(2-amino-5-iodothiazol-4-yl)-2-ethoxyiminoacetic acid (3.7 g) was added thereto. After it was stirred at  $-15^{\circ}\text{C}$  for 2 hours, diisopropyl ether (20 ml) was added thereto, and the resulting precipitate was collected by filtration (Precipitate A). On the other hand, 7 $\beta$ -amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate monohydrochloride (3.57 g) was suspended into ethyl acetate (20 ml) and N,N-dimethylformamide (30 ml), and then N-trimethylsilylacetamide (11.4 g) was added thereto. It was warmed at  $35^{\circ}\text{C}$  with stirring for 10 minutes to give a clear solution. The precipitate A which was synthesized before was added to this solution with stirring at  $5^{\circ}\text{C}$ , then it was stirred at the same temperature for an hour. After that, the reaction mixture was poured into a mixed solution of ethyl acetate (250 ml), diisopropyl ether (50 ml), and methanol (7 ml). The resulting precipitate was collected by filtration, and it was dissolved into water (100 ml) at pH 6.5. After the solution was adjusted to pH 4.0 with 1N-hydrochloric acid, it was subjected to column chromatography on Diaion HP-20 (90 ml) [Trademark; Mitsubishi Kasei Co.]. The column was washed with water (500 ml), and the object compound was eluted with 40% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7 $\beta$ -[(Z)-2-(2-amino-5-iodothiazol-4-yl)-2-ethoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.47 g).

IR (KBr) : 1774, 1614, 1529, 1039  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.29 (3H, t,  $J=7.0\text{Hz}$ ), 2.93, 3.19 (2H, ABq,  $J=17\text{Hz}$ ), 3.40-3.70 (2H, m), 4.12 (2H, q,  $J=7.0\text{Hz}$ ), 4.20-4.60 (2H, m), 5.00 (1H, d,  $J=4.8\text{Hz}$ ), 5.05, 5.22, (2H, ABq,  $J=15\text{Hz}$ ), 5.60 (1H, dd,  $J=4.8\text{Hz}$ , 8.5Hz), 5.82 (1H, d,  $J=3.2\text{Hz}$ ), 7.27 (2H, s), 7.38 (2H, s), 8.10 (1H, d,  $J=3.2\text{Hz}$ ), 9.42 (1H,

d, J=8.5Hz)

MS (FAB) m/z : 663 ( $M^+ + 1$ )

The following compounds (Examples 25 to 28) were obtained according to a similar manner to that of Example 24.

5

Example 25

7 $\beta$ -[(Z)-2-(2-Amino-5-bromothiazol-4-yl)-2-ethoxyimino-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

10 IR (KBr) : 1772, 1666, 1649, 1614, 1537, 1041  $\text{cm}^{-1}$   
NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.25 (3H, t, J=7.0Hz), 2.93, 3.20  
(2H, ABq, J=17Hz), 3.50-3.80 (2H, m), 4.11 (2H, q, J=7.0Hz), 4.20-4.60 (2H, m), 5.00 (1H, d, J=4.9Hz),  
15 5.12, 5.21 (2H, ABq, J=15Hz), 5.59 (1H, dd, J=4.9Hz, 8.4Hz), 5.81 (1H, d, J=3.2Hz), 7.23 (2H, s), 7.38 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.43 (1H, d, J=8.4Hz)

MS (FAB) m/z : 615 ( $M^+$ ), 617 ( $M^+ + 2$ )

20 Example 26

7 $\beta$ -[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-ethoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1612, 1539, 1038  $\text{cm}^{-1}$   
25 NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.23 (3H, t, J=7.0Hz), 2.93, 3.19  
(2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 4.10 (2H, q, J=7.0Hz), 4.20-4.60 (2H, m), 5.01 (1H, d, J=4.9Hz),  
5.05, 5.22 (2H, ABq, J=15Hz), 5.60 (1H, dd, J=4.9Hz, 8.5Hz), 5.82 (1H, d, J=3.2Hz), 7.27 (2H,  
30 s), 7.37 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.46 (1H, d, J=8.5Hz)

MS (FAB) m/z : 571 ( $M^+$ )

Example 27

35 7 $\beta$ -[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-

methoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1653, 1610, 1579, 1539, 1049  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 2.92, 3.20 (2H, ABq,  $J=17\text{Hz}$ ),  
3.4-3.8 (2H, m), 3.84 (3H, s), 4.2-4.6 (2H, m),  
5.00 (1H, d,  $J=4.9\text{Hz}$ ), 5.05, 5.21 (2H, ABq,  
 $J=15\text{Hz}$ ), 5.60 (1H, dd,  $J=4.9\text{Hz}$ ,  $8.5\text{Hz}$ ), 5.82 (1H,  
d,  $J=3.2\text{Hz}$ ), 7.28 (2H, s), 7.41 (2H, s), 8.10 (1H,  
d,  $J=3.2\text{Hz}$ ), 9.52 (1H, d,  $J=8.5\text{Hz}$ )

MS (FAB)  $m/z$  : 557 ( $\text{M}^+$ )

#### Example 28

7 $\beta$ -[(Z)-2-(2-Amino-5-methylthiothiazol-4-yl)-2-methoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1772, 1649, 1614, 1537, 1525, 1041  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 2.38 (3H, s), 2.93, 3.20 (2H, ABq,  
 $J=17\text{Hz}$ ), 3.40-3.80 (2H, m), 3.84 (3H, s), 4.20-4.60  
(2H, m), 5.00 (1H, d,  $J=4.9\text{Hz}$ ), 5.05, 5.22 (2H,  
ABq,  $J=16\text{Hz}$ ), 5.60 (1H, dd,  $J=4.9\text{Hz}$ ,  $8.5\text{Hz}$ ), 5.82  
(1H, d,  $J=3.2\text{Hz}$ ), 7.26 (2H, s), 7.32 (2H, s), 8.10  
(1H, d,  $J=3.2\text{Hz}$ ), 9.41 (1H, d,  $J=8.5\text{Hz}$ )

MS (FAB)  $m/z$  : 569 ( $\text{M}^++1$ )

The following compounds (Examples 29 to 32) were obtained according to a similar manner to that of Example 1.

#### Example 29

7 $\beta$ -[(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-propargyloxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 3.15-3.45 (2H+1H, m), 3.50-3.65 (2H,  
m), 4.10-4.45 (2H, m), 4.65-4.70 (2H, m), 5.00-5.35  
(2H, m), 5.07 (1H, d,  $J=4.9\text{Hz}$ ), 5.81 (1H, dd,  
 $J=4.9\text{Hz}$ ,  $8.4\text{Hz}$ ), 5.85 (1H, d,  $J=3.2\text{Hz}$ ), 8.00 (1H,

d, J=3.2Hz), 8.48 (1H, s), 9.73 (1H, d, J=8.4Hz),  
12.87 (1H, br s)

Example 30

5        7β-[(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-  
(methylthiomethoxyimino)acetamido]-3-[5-amino-1-(2-  
hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate

NMR (DMSO-d<sub>6</sub>, δ) : 2.10 (3H, s), 3.2-3.4 (2H, m), 4.05-  
4.50 (2H, m), 5.00-5.40 (2H+2H, m), 5.18 (1H, d,  
10        J=4.9Hz), 5.85 (1H, dd, J=4.9Hz, 8.4Hz), 5.90 (1H,  
d, J=3.1Hz), 8.12 (1H, d, J=3.1Hz), 8.52 (1H, s),  
9.65 (1H, d, J=8.4Hz), 12.9 (1H, br s)

Example 31

15        7β-[2-(2-Formylamino-5-chlorothiazol-4-yl)-2-  
oxoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]-  
methyl-3-cephem-4-carboxylate

NMR (DMSO-d<sub>6</sub>, δ) : 3.20-3.40 (2H, m), 2.45-2.60 (2H,  
m), 4.20-4.45 (2H, m), 5.10-5.40 (2H+1H, m),  
20        5.75-5.85 (1H+1H, m), 8.89 (2H, br s), 7.97 (1H, d,  
J=2.9Hz), 8.53 (1H, s), 9.84 (1H, d, J=7.9Hz),  
13.00 (1H, s)

Example 32

25        7β-[(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(1-  
tritylimidazol-4-yl)methoxyiminoacetamido]-3-[1-(2-  
hydroxyethyl)-5-amino-2-pyrazolio]methyl-3-cephem-4-  
carboxylate

NMR (DMSO-d<sub>6</sub>, δ) : 3.0-3.40 (2H, m), 3.50-3.75 (2H, m),  
30        4.0-4.50 (2H, m), 5.05-5.40 (5H, m), 5.80-5.95 (2H,  
m), 7.14 (1H, s), 7.30-7.60 (18H, m), 8.03 (1H, d,  
J=3.1Hz), 8.54 (1H, s), 9.74 (1H, d, J=8.4Hz), 12.9  
(1H, br s)

35        The following compounds (Examples 33 to 34) were

obtained according to a similar manner to that of Example 2.

Example 33

7 $\beta$ -[(Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(2-  
5 acetoxymethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-  
2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1776, 1726, 1673, 1631, 1542, 1390, 1280,  
1064 cm<sup>-1</sup>

10 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.00 (3H, s), 3.00-3.40 (2H, m),  
3.45-3.65 (2H, m), 4.10-4.50 (2H+2H+2H, m), 5.05  
(1H, d, J=4.9Hz), 5.00-5.30 (2H, m), 5.68 (1H, dd,  
J=4.9Hz, 7.9Hz), 5.83 (1H, d, J=2.8Hz), 7.32 (2H,  
br s), 8.09 (1H, d, J=2.8Hz), 8.53 (1H, s), 9.62  
(1H, d, J=7.9Hz)

Example 34

7 $\beta$ -[(Z)-2-(2-Formylamino-5-fluorothiazol-4-yl)-2-  
formyloxymethoxyimino)acetamido]-3-(5-amino-1-(2-hydroxyethyl)-2-  
pyrazolio]methyl-3-cephem-4-carboxylate

20 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 3.25-3.55 (2H, m), 3.60-3.70 (2H,  
m), 5.05-5.50 (1H+2H, m), 5.75 (1H, dd, J=5Hz,  
7.9Hz), 5.91 (1H, d, J=3Hz), 7.48 (2H, br s), 7.95  
(1H, s), 7.98 (1H, d, J=3Hz), 8.47 (1H, s), 9.75  
(1H, d, J=7.9Hz)

25 The following compounds (Examples 35 to 38) were  
obtained according to a similar manner to that of Example 5.

Example 35

30 7 $\beta$ -[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-  
(propargyloxymethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-  
2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1639, 1614, 1540, 1324, 1025 cm<sup>-1</sup>

35 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.89 and 3.20 (2H, ABq, J=17.3Hz),  
3.35-3.45 (1H, m), 3.45-3.65 (2H, m), 4.20-4.60



(2H, m), 4.60-4.80 (2H, m), 5.00 (1H, d, J=4.8Hz),  
5.05 and 5.18 (2H, ABq, J=18.4Hz), 5.60 (1H, dd,  
J=4.8Hz, 8.3Hz), 5.81 (1H, d, J=3.2Hz), 7.19 (2H,  
br s), 7.39 (2H, br s), 8.09 (1H, d, J=3.2Hz), 9.55  
5 (1H, d, J=8.3Hz)

#### Example 36

7 $\beta$ -[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-  
(methylthiomethoxyimino)acetamido]-3-[5-amino-1-(2-  
10 hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate  
IR (KBr) : 1772, 1614, 1538, 1390, 1355, 1062 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.20 (3H, s), 2.92 and 3.19 (2H,  
ABq, J=17.3Hz), 3.45-3.65 (2H, m), 4.20-4.55 (2H,  
m), 5.00 (1H, d, J=4.9Hz), 5.05-5.30 (2H, m), 5.25  
15 (2H, s), 5.60 (1H, dd, J=4.9Hz, 8.3Hz), 5.82 (1H,  
d, J=3.2Hz), 7.30 (2H, br s), 7.40 (2H, br s), 8.09  
(1H, d, J=3.2Hz), 9.56 (1H, d, J=8.3Hz)

#### Example 37

20 7 $\beta$ -[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-oxo-  
acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-  
3-cephem-4-carboxylate  
IR (KBr) : 1772, 1668, 1614, 1538, 1390, 1353, 1062 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.98 and 3.23 (2H, ABq, J=17.2Hz),  
25 3.25-3.65 (2H, m), 4.15-4.55 (2H, m), 5.04 (1H, d,  
J=4.9Hz), 5.07 and 5.25 (2H, ABq, J=18.2Hz), 5.63  
(1H, dd, J=4.9Hz, 7.9Hz), 5.82 (1H, d, J=2.8Hz),  
7.30 (2H, br s), 7.58 (2H, br s), 8.09 (1H, d,  
J=2.8Hz), 9.68 (1H, d, J=7.9Hz)

30

#### Example 38

7 $\beta$ -[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-(imidazol-4-  
yl)methoxyiminoacetamido]-3-[1-(2-hydroxyethyl)-5-amino-2-  
pyrazolio]methyl-3-cephem-4-carboxylate  
35 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.89 and 3.17 (2H, ABq, J=17.7Hz),

3.40-3.70 (2H, m), 4.20-4.55 (2H, m), 4.90-5.30  
(5H, m), 5.60 (1H, dd, J=8.4Hz, 4.8Hz), 5.82 (1H,  
d, J=3.1Hz), 7.08 (1H, s), 7.27 (2H, br s), 7.35  
(2H, br s), 7.57 (1H, s), 8.09 (1H, d, J=3.1Hz),  
9.64 (1H, d, J=8.4Hz)

MS (FAB) m/z : 624 (M+H)<sup>+</sup>

The following compounds (Examples 39 to 43) were  
obtained according to a similar manner to that of Example 7.

#### Example 39

7β-[(Z)-2-tert-Butoxycarbonylmethoxyimino-2-(2-amino-5-  
chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-  
2-pyrazolio]methyl-3-cephem-4-carboxylate

MS (FAB) m/z : 657.1 (M<sup>+</sup>)

#### Example 40

7β-[(Z)-2-Carbamoylmethoxyimino-2-(2-amino-5-  
chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-  
2-pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1676, 1616, 1539 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 2.89, 3.19 (2H, ABq, J=17.4Hz), 3.59  
(2H, br s), 4.2-4.6 (2H, m), 4.67 (2H, s), 5.00  
(1H, d, J=4.9Hz), 5.06, 5.20 (2H, ABq, J=15Hz),  
5.62 (1H, dd, J=8.6Hz, 4.9Hz), 5.81 (1H, d,  
J=3.1Hz), 7.26 (2H, br s), 7.41 (2H, br s), 8.10  
(1H, d, J=3.1Hz), 9.45 (1H, d, J=8.6Hz)

#### Example 41

7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-  
fluoromethoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-  
pyrazolio]methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1668, 1639, 1614 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 2.88, 3.21 (2H, ABq, J=17.3Hz),  
3.5-3.7 (2H, m), 4.2-4.6 (2H, m), 5.01 (1H, d,

J=4.9Hz), 5.07, 5.18 (2H, ABq, J=15.2Hz), 5.60 (1H, dd, J=8.3Hz, 4.9Hz), 5.71 (1H, d, J=56.1Hz), 5.81 (1H, d, J=3.2Hz), 7.22 (2H, br s), 7.48 (2H, br s), 8.10 (1H, d, J=3.2Hz), 9.72 (1H, d, J=8.3Hz)

5 MS (FAB) m/z : 575.0 ( $M^+$ )

#### Example 42

7 $\beta$ -[(Z)-2-Hydroxyimino-2-(2-amino-5-methylthiazol-4-yl)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-  
10 3-cephem-4-carboxylate

IR (KBr) : 3332, 1770, 1649, 1618  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.32 (3H, s), 2.88, 3.16 (2H, ABq, J=17.5Hz), 3.5-3.7 (2H, m), 4.2-4.5 (2H, m), 4.99 (1H, d, J=4.9Hz), 5.04, 5.21 (2H, ABq, J=15.2Hz),  
15 5.61 (1H, dd, J=8.6Hz, 4.9Hz), 5.81 (1H, d, J=3.2Hz), 6.81 (2H, br s), 7.30 (2H, br s), 8.09 (1H, d, J=3.2Hz), 9.19 (1H, d, J=8.6Hz)

MS (FAB) m/z : 523.1 ( $M^+ + 1$ )

#### 20 Example 43

7 $\beta$ -[(Z)-2-Methoxyimino-2-(2-amino-5-cyanothiazol-4-yl)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-  
3-cephem-4-carboxylate

IR (KBr) : 3390, 2210, 1772, 1649, 1618  $\text{cm}^{-1}$

25 NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.92, 3.22 (2H, ABq, J=17.3Hz), 3.5-3.7 (2H, m), 3.91 (3H, s), 4.2-4.6 (2H, m), 5.01 (1H, d, J=4.9Hz), 5.07, 5.21 (2H, ABq, J=15.1Hz), 5.60 (1H, dd, J=8.6Hz, 4.9Hz), 5.82 (1H, d, J=3.1Hz), 7.30 (2H, br s), 8.11 (1H, d, J=3.1Hz),  
30 8.34 (2H, br s), 9.61 (1H, d, J=8.6Hz)

MS (FAB) m/z : 548.0 ( $M^+ + 1$ )

#### Example 44

To a suspension of 7 $\beta$ -[(Z)-2-(2-tert-  
35 butoxycarbonylamino-5-chlorothiazol-4-yl)-2-pentenoylamino]-

3-[1-(2-hydroxyethyl)-5-amino-2-pyrazolio]methyl-3-cephem-4-carboxylate (750 mg) in dichloromethane (2.4 ml) and anisole (0.75 ml) was added dropwise trifluoroacetic acid (1.5 ml) at 20°C. The stirring was continued for 2 hours at the room temperature. The reaction mixture was poured into isopropyl ether (30 ml). The resulting powder was collected by filtration and dried in vacuo. The powder was dissolved in a water (50 ml), adjusted to pH 3.0 with aqueous sodium hydrogencarbonate and then subjected to column chromatography on HP-20 (30 ml) and eluted with 20% aqueous isopropyl alcohol. And then active fraction was lyophilized to give 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-pentenoylamino]-3-[1-(2-hydroxyethyl)-5-amino-2-pyrazolio]methyl-3-cephem-4-carboxylate (60 mg).

NMR (DMSO-d<sub>6</sub>, δ) : 0.98 (3H, t, J=7.5Hz), 2.2 (2H, qin, J=7.5Hz), 2.93 and 3.20 (2H, ABq, J=17.9Hz), 3.40-3.70 (2H, m), 4.20-4.60 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.05 and 5.20 (2H, ABq, J=15.8Hz), 5.58 (1H, dd, J=4.9Hz, 8.0Hz), 5.80 (1H, d, J=3.1Hz), 6.28 (1H, t, J=7.5Hz), 7.20 (2H, br s), 7.24 (2H, br s), 8.10 (1H, d, J=3.1Hz), 9.16 (1H, d, J=8.0Hz)

#### Example 45

A solution of 7β-[(Z)-2-(3-tert-butoxycarbonylallyloxyimino)-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.48 g) in 1.5 ml of dichloromethane and 0.5 ml of anisole was treated with 1 ml of trifluoroacetic acid. After 4 hours, the reaction mixture was poured into isopropyl ether. The precipitates were solved in 4 ml of methanol, and treated with hydrochloric acid (0.28 ml), and stirred for 4 hours at room temperature. The reaction mixture was dropped into ethyl acetate to get precipitates, which were purified by preparative HPLC to get 28 mg of 7β-[(Z)-2-(E)-3-

carboxyallyloxyimino)-2-(2-amino-5-chlorothiazol-4-yl)-  
acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-  
3-cephem-4-carboxylate.

IR (KBr) : 1772, 1651, 1541  $\text{cm}^{-1}$

5 NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 2.89, 3.19 (2H, ABq,  $J=16.9\text{Hz}$ ),  
3.5-3.7 (2H, m), 4.2-4.6 (2H, m), 4.76 (2H, d,  
 $J=2\text{Hz}$ ), 5.01 (1H, d,  $J=4.9\text{Hz}$ ), 5.07, 5.21 (2H, ABq,  
 $J=15\text{Hz}$ ), 5.61 (1H, dd,  $J=8.5\text{Hz}$ ,  $4.9\text{Hz}$ ), 5.81 (1H,  
d,  $J=3.2\text{Hz}$ ), 5.99 (1H, d,  $J=15.8\text{Hz}$ ), 6.84 (1H, dt,  
10  $J=15.8\text{Hz}$ ,  $2\text{Hz}$ ), 7.26 (2H, br s), 7.41 (2H, br s),  
8.10 (1H, d,  $J=3.2\text{Hz}$ ), 9.62 (1H, d,  $J=8.5\text{Hz}$ )  
MS (FAB)  $m/z$  : 627.0 ( $\text{M}^+$ )

#### Example 46

15 To a suspension of  $7\beta$ -[(Z)-2-(2-formylamino-5-  
chlorothiazol-4-yl)-2-(2-acetoxyethoxyimino)acetamido]-3-[5-  
amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-  
carboxylate (1.2 g) in methanol (12 ml) was added  
concentrated hydrochloric acid (0.86 ml) under stirring at  
20 25°C to 30°C. The stirring was continued for 3 hours at the  
20°C to 30°C. The reaction mixture was poured into a cooled  
water (100 ml), and adjusted to pH 3.5 with aqueous sodium  
hydrogen carbonate. To the resulting solution was evaporated  
in vacuo by removal of methanol. The residue was added  
25 3N-sodium hydroxide solution (3 ml) under ice-cooling with  
stirring and the mixture was stirred for 30 minutes at 5°C.  
The reaction mixture was adjusted to pH 3.5 with 6N-  
hydrochloric acid. The residue was subjected to column  
chromatography on HP-20 (50 ml), and eluted with 15%  
30 2-propanol and the eluate was lyophilized to give  $7\beta$ -[(Z)-2-  
(2-amino-5-chlorothiazol-4-yl)-2-(2-hydroxyethoxyimino)-  
acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-  
3-cephem-4-carboxylate (250 mg).

IR (KBr) : 1774, 1648, 1612, 1538, 1390, 1355, 1218,  
35 1066  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.94 and 3.18 (2H, ABq,  $J=17.3\text{Hz}$ ),  
3.40-3.65 (2H+2H, m), 4.00-4.20 (2H, m), 4.20-4.65  
(2H+1H, m), 5.01 (1H, d,  $J=4.9\text{Hz}$ ), 5.04 and 5.22  
(2H, ABq,  $J=18.2\text{Hz}$ ), 5.62 (1H, dd,  $J=4.9\text{Hz}$ ,  $7.9\text{Hz}$ ),  
5.81 (1H, d,  $J=2.9\text{Hz}$ ), 7.26 (2H, br s), 7.40 (2H,  
br s), 8.10 (1H, d,  $J=2.9\text{Hz}$ ), 9.43 (1H, d,  $J=7.9\text{Hz}$ )

#### Example 47

To a suspension of 7 $\beta$ -[(Z)-2-(2-formylamino-5-fluorothiazol-4-yl)-2-formyloxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (562 mg) in methanol (5.6 ml) was added concentrated hydrochloric acid (0.9 ml) under stirring at 25°C to 30°C. The stirring was continued for 3 hours at 20°C to 30°C. The reaction mixture was poured into an ice-cooled water (100 ml), and adjusted to pH 4.0 with aqueous sodium hydrogen carbonate. The resulting solution was evaporated in vacuo. The residue was subjected to column chromatography on HP-20 (50 ml), and eluted with 15% 2-propanol and the eluate was lyophilized to give 7 $\beta$ -[(Z)-2-(2-amino-5-fluorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (130 mg).

IR (KBr) : 1770, 1612, 1587, 1535, 1392, 1216,  
1066  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.90 and 3.18 (2H, ABq,  $J=16.9\text{Hz}$ ),  
3.45-3.60 (2H, m), 4.10-4.60 (2H, m), 4.99 (1H, d,  
 $J=4.8\text{Hz}$ ), 5.04 and 5.21 (2H, ABq,  $J=18.1\text{Hz}$ ), 5.61  
(1H, dd,  $J=4.8\text{Hz}$ ,  $7.9\text{Hz}$ ), 5.81 (1H, d,  $J=3\text{Hz}$ ), 6.99  
(2H, br s), 7.25 (2H, br s), 8.08 (1H, d,  $J=3\text{Hz}$ ),  
9.34 (1H, d,  $J=7.9\text{Hz}$ ), 11.50 (1H, s)

#### Example 48

A solution of 7 $\beta$ -[(Z)-2-tert-butoxycarbonylmethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (1.43

g) in 4.5 ml of dichloromethane and 1.5 ml of anisole was treated with trifluoroacetic acid (3 ml). After 1 hour, the reaction mixture was poured into isopropyl ether. The precipitates were purified by preparative HPLC to afford 0.15 g of 7 $\beta$ -[(Z)-2-carboxymethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 1772, 1749, 1649, 1541 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.88, 3.21 (2H, ABq, J=17.3Hz), 3.59 (2H, br s), 4.3-4.6 (2H, m), 4.48 (2H, br s), 5.06 (1H, d, J=4.9Hz), 5.1-5.3 (2H, m), 5.69 (1H, dd, J=9.2Hz, 4.9Hz), 5.83 (1H, d, J=3.1Hz), 7.33 (2H, br s), 7.42 (2H, br s), 8.07 (1H, d, J=3.1Hz), 10.25 (1H, d, J=9.2Hz)

MS (FAB) m/z : 601.0 (M<sup>+</sup>)

#### Example 49

A solution of 7 $\beta$ -[(Z)-2-(1-tert-butoxycarbonyl-1-methylethoxyimino)-2-(2-amino-5-chlorothiazol-4-yl)-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (4.15 g) in 12 ml of dichloromethane and 4 ml of anisole was treated with trifluoroacetic acid (8 ml). After 4 hours, the reaction mixture was poured into isopropyl ether. The precipitates were purified by column chromatography on HP-20 resin and by preparative HPLC to afford 160 mg of 7 $\beta$ -[(Z)-2-(1-carboxy-1-methylethoxyimino)-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 3332, 1774, 1651, 1541 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.44 (3H, s), 1.47 (3H, s), 2.95, 3.20 (2H, ABq, J=17.3Hz), 3.59 (2H, br s), 4.38 (2H, br s), 5.05 (1H, d, J=4.9Hz), 5.08, 5.22 (2H, ABq, J=15Hz), 5.66 (1H, dd, J=8.6Hz, 4.9Hz), 5.82 (1H, d, J=3.2Hz), 7.27 (2H, br s), 7.41 (2H, br s), 8.09 (1H, d, J=3.2Hz), 9.61 (1H, d, J=8.6Hz)

MS (FAB) m/z : 629.0 ( $M^+$ )

#### Example 50

Trifluoroacetic acid (0.3 ml) was added to a suspended  
5 solution of 7 $\beta$ -[(Z)-2-(2-amino-5-bromothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.15 g) in dichloromethane (0.6 ml) and anisole (0.15 ml) with stirring and ice-cooling. After it was stirred at 5°C for 10  
10 minutes, it was stirred at room temperature for 2 hours. The reaction mixture was poured into diisopropyl ether (30 ml), and the resulting precipitate was collected by filtration. The precipitate was dissolved into water (10 ml) at pH 7.0 with saturated of NaHCO<sub>3</sub> solution. After the solution was  
15 adjusted to pH 4.0 with 1N-hydrochloric acid, it was subjected to column chromatography on Diaion HP-20 (10 ml). The column was washed with water (50 ml), and the object compound was eluted with 40% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to  
20 give 7 $\beta$ -[(Z)-2-(2-amino-5-bromothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.11 g).

IR (KBr) : 1770, 1666, 1645, 1616, 1585, 1539 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.89, 3.17 (2H, ABq, J=17Hz),  
25 3.40-3.80 (2H, m), 4.20-4.60 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.04, 5.21 (2H, ABq, J=16Hz), 5.61 (1H, dd, J=4.9Hz, 8.5Hz), 5.81 (1H, d, J=3.2Hz), 7.26 (2H, s), 7.33 (2H, s), 8.09 (1H, d, J=3.2Hz), 9.31 (1H, d, J=8.5Hz)

30 MS (FAB) m/z : 587 ( $M^+$ ), 589 ( $M^++2$ )

#### Example 51

To a suspension of 7 $\beta$ -[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetamido]-3-[5-amino-1-(2-  
35 hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (12



g) and anisole (12 ml) in dichloromethane (40 ml) was added dropwise trifluoroacetic acid (36 ml) under ice-cooling with stirring and the mixture was stirred for 3 hours at 5°C to 10°C. The resulting solution was added to isopropyl ether (800 ml). The precipitate was collected by filtration and dried under reduced pressure. The powder was dissolved in water (400 ml), adjusted to pH 4.0 with aqueous sodium hydrogencarbonate and then subjected to column chromatography on HP-20 (300 ml), and eluted with 10% 2-propanol and the eluate was lyophilized to give 7 $\beta$ -[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (3.6 g).

IR (KBr) : 1772, 1612, 1538, 1392, 1353, 1064 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.90 and 3.28 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 4.20-4.60 (2H, m), 4.98 (1H, d, J=5.0Hz), 5.00 and 5.22 (2H, ABq, J=16Hz), 5.62 (1H, dd, J=5Hz, 8Hz), 5.81 (1H, d, J=3.0Hz), 7.10-7.25 (4H, m), 8.09 (1H, d, J=3.0Hz), 9.32 (1H, d, J=8Hz), 11.70 (1H, br s)

#### Example 52

A mixture of N,N-dimethylformamide (0.67 ml) and phosphorus oxychloride (0.8 ml) in tetrahydrofuran (23 ml) was stirred for 30 minutes at 5°C. (Z)-2-(2-Formylamino-5-chlorothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetic acid (2.27 g) was added thereto with stirring and ice-cooling, and the mixture was stirred for 30 minutes at 5°C to produce an activated acid solution. On the other hand, 7 $\beta$ -amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (2.7 g) was dissolved in a solution of mono-trimethyl silylacetamide (8 g) in N,N-dimethylformamide (27 ml) and tetrahydrofuran (27 ml). To the solution was at a time added the above obtained activated acid solution at 5°C, and the mixture was stirred for 1.5

hours at 5°C. The resulting solution was poured into ethyl acetate (500 ml). The precipitate was collected by filtration and dried under reduced pressure. The powder was suspended into methanol (30 ml), thereto was added concentrated hydrochloric acid (6.8 ml) at room temperature. After the reaction mixture was stirred at room temperature for 3 hours, the reaction mixture was poured into an ice-cooled water (100 ml) and adjusted to pH 3.5 with aqueous sodium hydrogen carbonate. The resulting solution was evaporated in vacuo by removal of MeOH. To the residual solution was subjected to column chromatography on HP-20 (50 ml), and eluted with 20% 2-propanol and the eluate was lyophilized to give 7β-[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (530 mg).

IR (KBr) : 1774, 1618, 1538, 1359, 1220, 1062 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 1.80-2.55 (4H, m), 2.93 and 3.17 (2H, ABq, J=17Hz), 3.40-3.83 (2H, m), 4.20-4.60 (2H, m), 4.98 (1H, d, J=5.0Hz), 5.00-5.30 (3H, m), 5.58 (1H, dd, J=5Hz, 8.5Hz), 5.82 (1H, d, J=3.2Hz), 5.92 (1H, m), 6.07 (1H, m), 7.26 (2H, s), 7.41 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.42 (1H, d, J=8.5Hz)

### Example 53

Phosphorus oxychloride (3.52 g) was added to a mixed solution of N,N-dimethylformamide (1.78 ml) and ethyl acetate (5.4 ml) with stirring and ice-cooling. After it was stirred at 5°C for 30 minutes, (Z)-2-(2-formylamino-5-bromothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetic acid (7.5 g) and ethyl acetate (12 ml) was added thereto at the same temperature. After the reaction mixture was stirred at 5°C for 30 minutes, this is referred to as solution (A). On the other hand, N-trimethylsilylacetamide (12.3 g) was added to a suspended mixture of 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate monohydrochloride

(3.87 g) in N,N-dimethylformamide (20 ml) and ethyl acetate (50 ml) at room temperature, and the suspended mixture was warmed at 35°C with stirring for 10 minutes to give a clear solution. The above solution (A) was added to this clear solution with stirring at 5°C, then it was stirred at the same temperature for 2 hours. After that, the reaction mixture was poured into a mixed solution of ethyl acetate (300 ml), diisopropyl ether (50 ml), and methanol (10 ml). The resulting precipitate was collected by filtration, and it was suspended into methanol (60 ml). Concentrated hydrochloric acid (4.5 ml) was added thereto at room temperature. After the reaction mixture was stirred at room temperature for 3 hours, it was poured into water (60 ml), and the solution was adjusted to pH 4.0 with potassium carbonate. It was concentrated to remove methanol, and it was subjected to column chromatography on Diaion HP-20 (100 ml) [Trademark; Mitsubishi Kasei Co.]. The column was washed with water (500 ml), and the object compound was eluted with 40% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7 $\beta$ -[(Z)-2-(2-amino-5-bromothiazol-4-yl)-2-(3-cyclopentenyl)oxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.22 g).

IR (KBr) : 1772, 1668, 1645, 1616, 1537 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.80-2.55 (4H, m), 2.93, 3.17 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 4.20-4.60 (2H, m), 4.99 (1H, d, J=4.9Hz), 5.00-5.30 (3H, m), 5.58 (1H, dd, J=4.9Hz, 8.4Hz), 5.82 (1H, d, J=3.2Hz), 5.92 (1H, m), 6.07 (1H, m), 7.26 (2H, s), 7.41 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.42 (1H, d, J=8.4Hz)

MS (FAB) m/z : 653 (M<sup>+</sup>), 655 (M<sup>+</sup>+2)

#### Example 54

To an ice-cooling solution of N,N-dimethylformamide (0.20 ml) and ethyl acetate (1.0 ml) was added phosphorus

oxychloride (0.385 g). After it was stirred under ice-cooling for 30 minutes, (Z)-2-(2-formylamino-5-bromothiazol-4-yl)-2-(1-trityl-1H-1,2,3-triazol-5-yl)thiomethoxyimino-acetic acid (1.5 g) was added thereto, and it was stirred at the same temperature for one hour. On the other hand, N-trimethylsilylacetamide (3.03 g) was added to a suspension of 7 $\beta$ -amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (0.95 g) in ethyl acetate (5 ml) and N,N-dimethylformamide (10 ml) at room temperature, and it was warmed at 40°C. After it became clear, the reaction mixture was cooled below 5°C, the above solution of acetic acid derivative was added thereto. After it was stirred under ice-cooling for one hour, it was poured into ethyl acetate (40 ml) and diisopropyl ether (300 ml), and the resulting precipitate was collected by filtration. To a suspension of the precipitate in methanol (25 ml) was added concentrated hydrochloric acid (1.13 ml), and it was stirred at room temperature for 3 hours. The reaction mixture was poured into ethyl acetate (20 ml) and diisopropyl ether (80 ml), and the resulting precipitate was collected by filtration. It was dissolved into water (60 ml) at pH 4, subjected to column chromatography on Diaion HP-20 (15 ml). The column was washed with water (150 ml), then the object compound was eluted with 15% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7 $\beta$ -[(Z)-2-(2-amino-5-bromothiazol-4-yl)-2-(1H-1,2,3-triazol-5-yl)thiomethoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.21 g).

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.86, 3.11 (2H, ABq, J=17Hz), 3.60 (2H, s), 4.30-4.50 (2H, m), 4.99 (1H, d, J=4.9Hz), 5.00-5.25 (2H, m), 5.44 (2H, s), 5.54 (1H, dd, J=4.9Hz, 7.9Hz), 5.81 (1H, d, J=3.2Hz), 7.22 (2H, s), 7.45 (2H, s), 8.01 (1H, s), 8.11 (1H, d, J=3.2Hz), 9.39 (1H, d, J=7Hz)

MS (FAB) m/z : 701 ( $M^+ + 1$ )

#### Example 55

To a solution of the mixture of (Z)-2-(1-trityl-1H-tetrazol-5-ylmethoxyimino)-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid and (Z)-2-(2-trityl-2H-tetrazol-5-ylmethoxyimino)-2-(2-formylamino-5-chlorothiazol-4-yl)acetic acid (2.14 g) in 22 ml of N,N-dimethylacetamide, powdered potassium carbonate (0.52 g) and methanesulfonyl chloride (0.85 g) were added stepwise at 0°C. On the other hand, a suspension of 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (1.40 g) in 14 ml of N,N-dimethylacetamide was treated portionwise with N-(trimethylsilyl)acetamide (2.94 g) at room temperature. Both reaction mixture were combined at 0°C and stirred for 5.5 hours. The reaction was quenched by dropping into ethyl acetate to get precipitates, and which were dissolved in 10 ml of methanol and treated with concentrated hydrochloric acid. The reaction was quenched by dropping into ethyl acetate to get precipitates, and which were purified by column chromatography on HP-20 resin and preparative liquid chromatography to get 0.06 g of 7β-[(Z)-2-(tetrazol-5-ylmethoxyimino)-2-(5-chloro-2-aminothiazol-4-yl)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

IR (KBr) : 3412, 1772, 1635  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.86, 3.17 (2H, ABq,  $J=17.4\text{Hz}$ ), 3.59 (2H, m), 4.34 (2H, m), 5.00 (1H, d,  $J=4.9\text{Hz}$ ), 5.15 (2H, m), 5.33 (2H, s), 5.65 (1H, dd,  $J=8.5\text{Hz}$ , 4.9Hz), 5.83 (1H, d,  $J=3.2\text{Hz}$ ), 7.21 (2H, br s), 7.39 (2H, br s), 8.05 (1H, d,  $J=3.2\text{Hz}$ ), 10.03 (1H, d,  $J=8.5\text{Hz}$ )

MS (FAB) m/z : 625.0

#### Example 56

Potassium carbonate (0.71 g) was added to an ice-cooling solution of (Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-(1-methylpyrazol-4-yl)methoxyiminoacetic acid (2.19 g) in N,N-dimethylacetamide (20 ml), and it was stirred at 5-10°C for 20 minutes. After methanesulfonyl chloride (1.17 g) was added dropwise to the solution below 10°C, it was stirred under ice-cooling for one hour. On the other hand, N-trimethylsilylacetamide (7.1 g) was added to a suspension of 7 $\beta$ -amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (2.23 g) in ethyl acetate (10 ml) and N,N-dimethylformamide (20 ml) at room temperature, and it was warmed at 40°C. After it became clear, the reaction mixture was cooled below 5°C, the above N,N-dimethylacetamide solution was added thereto. After it was stirred under ice-cooling for one hour, it was poured into ethyl acetate (50 ml) and diisopropyl ether (400 ml), and the resulting precipitate was collected by filtration. To a suspension of the precipitate in methanol (20 ml) was added concentrated hydrochloric acid (2 ml), and it was stirred at room temperature for 2 hours. The reaction mixture was poured into ethyl acetate (20 ml) and diisopropyl ether (80 ml), then the resulting precipitate was collected by filtration. It was dissolved into water (70 ml) at pH 4, and subjected to column chromatography on Diaion HP-20 (20 ml). The column was washed with water (200 ml), then the object compound was eluted with 15% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7 $\beta$ -[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(1-methylpyrazol-4-yl)methoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.45 g).

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.88, 3.18 (2H, ABq, J=17Hz), 3.50-3.65 (2H, m), 3.78 (3H, s), 4.30-4.60 (2H, m), 4.96 (2H, s), 4.97 (1H, d, J=4.9Hz), 5.03-5.25 (2H, m), 5.59 (1H, dd, J=4.9Hz, 8.4Hz), 5.82 (1H, d,

J=3.2Hz), 7.27 (2H, s), 7.35 (2H, s), 7.42 (1H, s),  
7.69 (1H, s), 8.10 (1H, d, J=3.2Hz), 9.47 (1H, d,  
J=8.4Hz)

MS (FAB) m/z : 637 (M<sup>+</sup>)

5

#### Example 57

Potassium carbonate (332 mg) was added to an ice-cooling solution of (Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-(1-tert-butoxycarbonylpyrazol-4-yl)methoxyiminoacetic acid (1.72 g) in N,N-dimethylacetamide (17 ml), and it was stirred at 10  
5-10°C for 10 minutes. After methanesulfonyl chloride (0.50 g) was added dropwise to the solution below 10°C, it was stirred under ice-cooling for one hour. On the other hand, N-trimethylsilylacetamide (4.2 g) was added to a solution of  
15 7β-amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (1.32 g) in ethyl acetate (8 ml) and N,N-dimethylformamide (16 ml) at room temperature, and it was warmed at 40°C. After it became clear, the reaction mixture was cooled below 5°C, and the above  
20 N,N-dimethylacetamide solution was added thereto. After it was stirred under ice-cooling for one hour, it was poured into ethyl acetate (40 ml) and diisopropyl ether (350 ml), and the resulting precipitate was collected by filtration. To a suspension of the precipitate in methanol (20 ml) was  
25 added concentrated hydrochloric acid (1.67 ml), and it was stirred at room temperature for 2 hours. The reaction mixture was poured into ethyl acetate (20 ml) and diisopropyl ether (80 ml), then the resulting precipitate was collected by filtration. To a suspension of the precipitate in  
30 dichloromethane (2 ml) and anisole (1 ml) was added trifluoroacetic acid (3 ml) under ice-cooling, then it was stirred at room temperature for one hour. The reaction mixture was poured into diisopropyl ether (40 ml), and the resulting precipitate was collected by filtration. It was  
35 dissolved into water (80 ml) at pH 4, and subjected to column

chromatography on Diaion HP-20 (25 ml). The column was washed with water (250 ml), then the object compound was eluted with 15% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give

5 7 $\beta$ -[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(pyrazol-4-yl)-methoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.22 g).

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.88, 3.18 (2H, ABq, J=17Hz), 3.50-3.70 (2H, m), 4.20-4.60 (2H, m), 4.90-5.30 (5H, m),

10 5.59 (1H, dd, J=4.8Hz, J=8.6Hz), 5.82 (1H, d, J=3.2Hz), 7.25 (2H, s), 7.35 (2H, s), 7.63 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.48 (1H, d, J=8.6Hz)

MS (FAB) m/z : 623 (M<sup>+</sup>)

15 Example 58

Phosphorus pentachloride (1.68 g) was suspended into dichloromethane (18 ml), then it was cooled to -20°C, and (Z)-2-(2-amino-5-iodothiazol-4-yl)-2-acetoxyminoacetic acid (2.6 g) was added thereto. After it was stirred at -15°C for

20 2 hours, diisopropyl ether (20 ml) was added thereto, and the resulting precipitate was collected by filtration. On the other hand, 7 $\beta$ -amino-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate monohydrochloric acid salt (2.14 g) was suspended into ethyl acetate (15 ml) and

25 N,N-dimethylformamide (25 ml), and then N-trimethylsilyl-acetamide (6.8 g) was added thereto. It was warmed at 35°C with stirring for 10 minutes to give a clear solution. The precipitate which was synthesized above was added to the clear solution with stirring at 5°C, then it was stirred at

30 the same temperature for an hour. After that, the reaction mixture was poured into a mixed solution of ethyl acetate (200 ml), diisopropyl ether (50 ml), and methanol (50 ml). The resulting precipitate was collected by filtration, and it was suspended into methanol (25 ml). Concentrated

35 hydrochloric acid (2.0 ml) was added thereto at room



temperature. After the reaction mixture was stirred at room temperature for 2 hours, it was poured into water (25 ml), and the solution was adjusted to pH 4.0 with potassium carbonate. It was concentrated to remove methanol, and it was subjected to column chromatography on Diaion HP-20 (90 ml) [Trademark; Mitsubishi Kasei Co.]. The column was washed with water (500 ml), and the object compound was eluted with 40% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7 $\beta$ -[(Z)-2-(2-amino-5-iodothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.18 g).

IR (KBr) : 1770, 1645, 1614, 1537  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.91, 3.18 (2H, ABq,  $J=17\text{Hz}$ ), 3.40-3.80 (2H, m), 4.20-4.60 (2H, m), 5.00 (1H, d,  $J=4.9\text{Hz}$ ), 5.05, 5.22 (2H, ABq,  $J=16\text{Hz}$ ), 5.62 (1H, dd,  $J=4.9\text{Hz}$ ,  $8.5\text{Hz}$ ), 5.82 (1H, d,  $J=3.1\text{Hz}$ ), 7.29 (4H, s), 8.09 (1H, d,  $J=3.1\text{Hz}$ ), 9.25 (1H, d,  $J=8.5\text{Hz}$ ), 11.64 (1H, s)

MS (FAB)  $m/z$  : 635 ( $M^++1$ )

#### Example 59

N-Bromosuccinimide (0.68 g) was added to a solution of 7 $\beta$ -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (1.0 g) in N,N-dimethylacetamide (10 ml) with ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ethyl acetate (80 ml) and diisopropyl ether (20 ml), and the resulting precipitate was collected by filtration. The precipitate was dissolved into water (40 ml) at pH 6.5, and then the solution was adjusted to pH 4.0 with 1N-hydrochloric acid. It was subjected to column chromatography on Diaion HP-20 (30 ml) [Trademark; Mitsubishi Kasei Co.]. The column was washed with water (200 ml), and the object compound was

eluted with 30% aqueous 2-propanol. The active fractions were collected, concentrated, and lyophilized to give 7 $\beta$ -[(Z)-2-(2-amino-5-bromothiazol-4-yl)-2-methoxyimino-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate (0.25 g).

IR (KBr) : 1770, 1649, 1614, 1537 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.92, 3.20 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 3.84 (3H, s), 4.20-4.60 (2H, m), 5.00 (1H, d, J=4.9Hz), 5.06, 5.21 (2H, ABq, J=15Hz), 5.60 (1H, dd, J=4.9Hz, 8.5Hz), 5.82 (1H, d, J=3.2Hz), 7.27 (2H, s), 7.41 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.49 (1H, d, J=8.5Hz)

MS (FAB) m/z : 601 (M<sup>+</sup>), 603 (M<sup>+</sup>+2)

#### Example 60

7 $\beta$ -[(Z)-2-(2-Amino-5-iodothiazol-4-yl)-2-methoxyimino-acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate was obtained according to a similar manner to that of Example 59.

IR (KBr) : 1772, 1649, 1614, 1535, 1039 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.92, 3.20 (2H, ABq, J=17Hz), 3.40-3.80 (2H, m), 3.86 (3H, s), 4.20-4.60 (2H, m), 4.99 (1H, d, J=4.8Hz), 5.06, 5.20 (2H, ABq, J=15Hz), 5.59 (1H, dd, J=4.8Hz, 8.5Hz), 5.82 (1H, d, J=3.2Hz), 7.27 (2H, s), 7.38 (2H, s), 8.10 (1H, d, J=3.2Hz), 9.43 (1H, d, J=8.5Hz)

MS (FAB) m/z : 649 (M<sup>+</sup>+1)

The following compounds (Examples 61 to 66) were obtained according to a similar manner to that of Example 3.

#### Example 61

7 $\beta$ -[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-methoxyiminoacetamido]-3-(4,5,6,7-tetrahydro-1-pyrazolo-[1,5-a]pyrimidinio)methyl-3-cephem-4-carboxylate

IR (KBr) : 1770, 1619, 1538, 1438, 1243, 1037  $\text{cm}^{-1}$   
NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 1.85-2.30 (2H, m), 3.1-3.80 (4H, m),  
3.84 (3H, s), 4.00-4.25 (2H, m), 4.94 and 5.26 (2H,  
ABq,  $J=15\text{Hz}$ ), 4.99 (1H, d,  $J=4.8\text{Hz}$ ), 5.58 (1H, dd,  
5  $J=8.3\text{Hz}$ ,  $4.8\text{Hz}$ ), 5.80 (1H, d,  $J=3.1\text{Hz}$ ), 7.39 (2H,  
br s), 7.94 (1H, br s), 8.07 (1H, d,  $J=3.1\text{Hz}$ ), 9.48  
(1H, d,  $J=8.3\text{Hz}$ )

#### Example 62

10 7 $\beta$ -[(Z)-2-Ethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)-  
acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]-  
methyl-3-cephem-4-carboxylate

IR (KBr) : 3390, 1772, 1608, 1539  $\text{cm}^{-1}$

15 NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 1.24 (3H, t,  $J=7.0\text{Hz}$ ), 3.11, 3.33  
(2H, ABq,  $J=17.2\text{Hz}$ ), 4.02 (2H, t,  $J=8.8\text{Hz}$ ), 4.11  
(2H, q,  $J=7.0\text{Hz}$ ), 4.26 (1H, q,  $J=8.8\text{Hz}$ ), 4.52 (1H,  
q,  $J=8.8\text{Hz}$ ), 4.97, 5.08 (2H, ABq,  $J=14.6\text{Hz}$ ), 5.01  
(1H, d,  $J=4.9\text{Hz}$ ), 5.59 (1H, dd,  $J=4.9$ ,  $8.5\text{Hz}$ ), 5.87  
(1H, d,  $J=3.0\text{Hz}$ ), 7.38 (2H, br s), 8.23 (1H, d,  
20  $J=3.0\text{Hz}$ ), 9.44 (1H, d,  $J=8.5\text{Hz}$ )

MS (FAB)  $m/z$  : 553.0 ( $\text{M}^+$ ), 555.0 ( $\text{M}^++2$ )

#### Example 63

25 7 $\beta$ -[(Z)-2-Ethoxyimino-2-(2-amino-5-bromothiazol-4-yl)-  
acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]-  
methyl-3-cephem-4-carboxylate

IR (KBr) : 3390, 1770, 1608, 1537  $\text{cm}^{-1}$

30 NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 1.25 (3H, t,  $J=7.0\text{Hz}$ ), 3.11, 3.32  
(2H, ABq,  $J=17.0\text{Hz}$ ), 4.02 (2H, m), 4.11 (2H, q,  
 $J=7.0\text{Hz}$ ), 4.26 (1H, q,  $J=8.9\text{Hz}$ ), 4.52 (1H, q,  
 $J=8.3\text{Hz}$ ), 4.9-5.1 (2H, m), 5.01 (1H, d,  $J=4.9\text{Hz}$ ),  
5.59 (1H, dd,  $J=4.9$ ,  $8.5\text{Hz}$ ), 5.87 (1H, d,  $J=3.0\text{Hz}$ ),  
7.42 (2H, br s), 7.8 (1H, br s), 8.23 (1H, d,  
 $J=3.0\text{Hz}$ ), 9.44 (1H, d,  $J=8.5\text{Hz}$ )

35 MS (FAB)  $m/z$  : 597.1 ( $\text{M}^+$ )

Example 64

7 $\beta$ -[(Z)-2-Methoxyimino-2-(2-amino-5-chlorothiazol-4-yl)-acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]-methyl-3-cephem-4-carboxylate

5 IR (KBr) : 3392, 1770, 1608, 1539 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 3.12, 3.34 (2H, ABq, J=17.3Hz), 3.84 (3H, s), 4.02 (2H, m), 4.26 (1H, q, J=8.7Hz), 4.52 (1H, q, J=8.3Hz), 4.95-5.12 (2H+1H, m), 5.60 (1H, dd, J=4.8, 8.5Hz), 5.87 (1H, d, J=2.9Hz), 7.42 (2H, br s), 8.03 (1H, br s), 8.25 (1H, d, J=2.9Hz), 9.49 (1H, d, J=8.5Hz)

10 MS (FAB) m/z : 539.1 (M<sup>+</sup>)

Example 65

15 7 $\beta$ -[(Z)-2-Acetoxyimino-2-(2-amino-5-chlorothiazol-4-yl)-acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]-methyl-3-cephem-4-carboxylate

MS (FAB) m/z : 567.1 (M<sup>+</sup>), 569.2 (M<sup>+</sup>+2)

20 Example 66

7 $\beta$ -[(Z)-2-Cyanomethoxyimino-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]methyl-3-cephem-4-carboxylate

MS (FAB) m/z : 592.1 (M<sup>+</sup>)

25

Example 67

To a solution of 7 $\beta$ -amino-3-(4,5,6,7-tetrahydro-1-pyrazolo[1,5-a]pyrimidinio)methyl-3-cephem-4-carboxylate (1 g) and monotrimethylsilylacetamide (3.37 g) in a mixture of tetrahydrofuran (10 ml) and N,N-dimethylformamide (10 ml) was added (Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-ethoxyiminoacetyl chloride hydrochloride (0.85 g) in one portion at 5°C under stirring. The stirring was continued for 1.5 hours at the same temperature. The reaction mixture was poured into ethyl acetate (300 ml) to form the

30

35

precipitates and then the resulting precipitates were collected by filtration and dried in vacuo. The powder was dissolved in a water (50 ml), and adjusted to pH 3.0 with aqueous sodium hydrogencarbonate. Subsequently, the solution was subjected to column chromatography on HP-20 [Trademark; Mitsubishi Kasei Corporation] (30 ml) and eluted with 20% aqueous isopropyl alcohol, and the eluate was lyophilized to give 7 $\beta$ -[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-ethoxyimino]-acetamido-3-(4,5,6,7-tetrahydro-1-pyrazolo[1,5-a]-pyrimidinio)methyl-3-cephem-4-carboxylate (249 mg).

IR (KBr) : 1774, 1666, 1619, 1538, 1322, 1037 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.23 (3H, t, J=7.1Hz), 1.80-2.25 (2H, m), 3.0-3.4 (4H, m), 4.00-4.30 (4H, m), 4.86 and 5.28 (2H, ABq, J=15Hz), 5.00 (1H, d, J=4.9Hz), 5.61 (1H, dd, J=8.4Hz, 4.9Hz), 5.80 (1H, d, J=3.1Hz), 7.39 (2H, br s), 8.02 (1H, br s), 8.06 (1H, d, J=3.1Hz), 9.48 (1H, d, J=8.4Hz)

#### Example 68

7 $\beta$ -[(Z)-2-Fluoromethoxyimino-2-(5-chloro-2-formylaminothiazol-4-yl)acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]methyl-3-cephem-4-carboxylate was obtained according to a similar manner to that of Example 22.

#### Example 69

To a solution of 7 $\beta$ -amino-3-(4,5,6,7-tetrahydro-1-pyrazolo[1,5-a]pyrimidinio)methyl-3-cephem-4-carboxylate (3 g) and monotrimethylsilylacetamide (10.1 g) in a mixture of tetrahydrofuran (30 ml) and N,N-dimethylformamide (30 ml) was added (Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-acetoxyiminoacetyl chloride (2.86 g) in one portion at 5°C under stirring. The stirring was continued for 1.5 hours at the same temperature. The reaction mixture was poured into ethyl acetate (800 ml) to form the precipitates and then the resulting precipitates were collected by filtration, and

dried in vacuo to give 7β-[(Z)-2-(2-formylamino-5-chlorothiazol-4-yl)-2-acetoxyimino]acetamido-3-(4,5,6,7-tetrahydro-1-pyrazolo[1,5-a]pyrimidinio)methyl-3-cephem-4-carboxylate (5 g).

5        NMR (DMSO-d<sub>6</sub>, δ) : 2.00-2.25 (2H, m), 2.21 (3H, s),  
         3.25-3.65 (4H, m), 4.0-4.35 (2H, m), 5.20-5.45 (3H,  
         m), 5.8-6.0 (2H, m), 8.0 (1H, br s), 8.08 (1H, d,  
         J=3.1Hz), 9.98 (1H, d, J=8.3Hz), 13.0 (1H, br s)

10        The following compounds (Examples 70 to 72) were  
         obtained according to a similar manner to that of Example 7.

Example 70

15        7β-[(Z)-2-Fluoromethoxyimino-2-(2-amino-5-chlorothiazol-  
         4-yl)acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]-  
         pyrazolio)]methyl-3-cephem-4-carboxylate

         IR (KBr) : 3429, 1770, 1610 cm<sup>-1</sup>

20        NMR (DMSO-d<sub>6</sub>, δ) : 3.09, 3.34 (2H, ABq, J=17.1Hz), 4.02  
         (2H, t, J=8.1Hz), 4.26 (1H, q, J=8.1Hz), 4.54 (1H,  
         q, J=8.1Hz), 4.9-5.1 (2H, m), 5.02 (1H, d,  
         J=4.8Hz), 5.57 (1H, s), 5.60 (1H, dd, J=4.8,  
         8.3Hz), 5.86 (1H, s), 5.87 (1H, d, J=3.0Hz), 7.46  
         (2H, br s), 8.24 (1H, d, J=3.0Hz), 9.67 (1H, d,  
         J=8.3Hz)

25        MS (FAB) m/z : 557.0 (M<sup>+</sup>)

Example 71

30        7β-[(Z)-2-Hydroxyimino-2-(2-amino-5-chlorothiazol-4-yl)-  
         acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]pyrazolio)]-  
         methyl-3-cephem-4-carboxylate

         IR (KBr) : 3390, 1772, 1603 cm<sup>-1</sup>

35        NMR (DMSO-d<sub>6</sub>, δ) : 3.08, 3.31 (2H, ABq, J=17.2Hz), 4.01  
         (2H, m), 4.25 (1H, q, J=8.7Hz), 4.53 (1H, q,  
         J=8.0Hz), 5.00 (1H, d, J=4.7Hz), 4.97, 5.08 (2H,  
         ABq, J=14.4Hz), 5.61 (1H, dd, J=4.7, 8.2Hz), 5.87

(1H, d, J=2.9Hz), 7.31 (2H, br s), 8.23 (1H, d, J=2.9Hz), 9.31 (1H, d, J=8.2Hz)

MS (FAB) m/z : 525.2 (M<sup>+</sup>+1)

5     Example 72

7β-[(Z)-2-Cyanomethoxyimino-2-(2-amino-5-chlorothiazol-4-yl)acetamido]-3-[2,3-dihydro-5-(1H-imidazo[1,2-b]-pyrazolio)]methyl-3-cephem-4-carboxylate

IR (KBr) : 3413, 1772, 1606 cm<sup>-1</sup>

10     NMR (DMSO-d<sub>6</sub>, δ) : 3.09, 3.35 (2H, ABq, J=17.2Hz), 4.02 (2H, t, J=8.6Hz), 4.26 (1H, q, J=8.6Hz), 4.53 (1H, q, J=8.6Hz), 5.0-5.1 (2H+2H+1H, m), 5.59 (1H, dd, J=4.8Hz, 8.4Hz), 5.87 (1H, d, J=3.0Hz), 7.47 (2H, br s), 7.84 (1H, br s), 8.24 (1H, d, J=3.0Hz), 9.68 (1H, d, J=8.4Hz)

15     MS (FAB) m/z : 564.0 (M<sup>+</sup>), 566.0 (M<sup>+</sup>+2)

Example 73

20     7β-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(4,5,6,7-tetrahydro-1-pyrazolo-[1,5-a]pyrimidinio)methyl-3-cephem-4-carboxylate was obtained according to a similar manner to that of Example 5.

IR (KBr) : 1772, 1619, 1538, 1520, 1245, 1178 cm<sup>-1</sup>

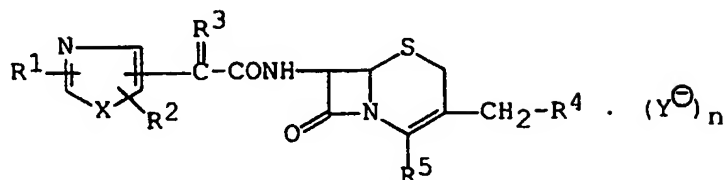
25     NMR (DMSO-d<sub>6</sub>, δ) : 1.8-2.20 (2H, m), 2.95-3.80 (4H, m), 4.0-4.25 (2H, m), 4.96 and 5.28 (2H, ABq, J=15Hz), 4.99 (1H, d, J=5Hz, 8.4Hz), 5.80 (1H, d, J=3.1Hz), 7.31 (2H, br s), 8.03 (1H, br s), 8.06 (1H, d, J=3.1Hz), 9.31 (1H, d, J=8.41Hz), 11.78 (1H, br s)

30

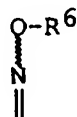
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## C L A I M S

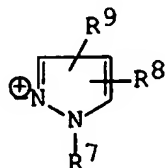
1. A cephem compound of the formula :



wherein  $R^1$  is amino or a protected amino,  
 $R^2$  is halogen, lower alkyl, cyano or  
 lower alkylthio,  
 $R^3$  is a group of the formula :



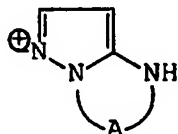
[wherein  
 $R^6$  is hydrogen, lower alkyl which may have  
 one or more substituent(s), lower  
 alkenyl which may have one or more  
 substituent(s), lower alkynyl,  
 cyclo(lower)alkenyl, or acyl],  
 lower alkylidene or oxo,  
 $R^4$  is a group of the formula :



[wherein  
 $R^7$  is hydroxy(lower)alkyl or protected  
 hydroxy(lower)alkyl,



$R^8$  is amino or a protected amino, and  
 $R^9$  is hydrogen or lower alkyl],  
 or a group of the formula :

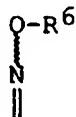


(wherein A is lower alkylene),  
 10  $R^5$  is  $-COO^\ominus$ , carboxy or a protected carboxy,  
 X is  $-S-$  or  $-O-$ ,  
 $Y^\ominus$  is an anion, and  
 n is 0 or 1,

with proviso that

15 (i) when  $R^5$  is  $-COO^\ominus$ , then n is 0, and  
 (ii) when  $R^5$  is carboxy or a protected carboxy,  
 then n is 1,  
 and a salt thereof.

20 2. A compound of claim 1, wherein  
 $R^3$  is a group of the formula :

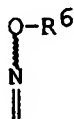


{wherein  $R^6$  is hydrogen;

lower alkyl which may have 1 to 3  
 substituent(s) selected from the group  
 consisting of halogen, cyano, aryl, lower  
 30 alkylthio, carboxy, protected carboxy,  
 hydroxy(lower)alkyl, protected  
 hydroxy(lower)alkyl, heterocyclic group  
 which may have 1 to 3 substituent(s)  
 selected from the group consisting of  
 35 lower alkyl and ar(lower)alkyl, and

heterocyclicthio;  
lower alkenyl which may have 1 to 3  
substituent(s) selected from the group  
consisting of carboxy and protected  
carboxy;  
lower alkynyl;  
cyclo(lower)alkenyl; or acyl],  
lower alkylidene or oxo.

3. A compound of claim 2, wherein  
R<sup>1</sup> is amino, lower alkanoylamino, lower  
alkoxycarbonylamino or triphenyl(lower)alkylamino,  
R<sup>3</sup> is a group of the formula :



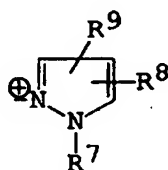
[wherein R<sup>6</sup> is hydrogen; lower alkyl; halo(lower)alkyl;  
dihalo(lower)alkyl; cyano(lower)alkyl;  
triphenyl(lower)alkyl; lower  
alkylthio(lower)alkyl;  
carboxy(lower)alkyl; lower  
alkoxycarbonyl(lower)alkyl;  
carbamoyl(lower)alkyl;  
hydroxy(lower)alkyl;  
lower alkanoyloxy(lower)alkyl;  
heterocyclic(lower)alkyl,  
in which heterocyclic moiety is  
unsaturated 3 to 8-membered  
heteromonocyclic group containing 1 to 4  
nitrogen atom(s), which may have lower  
alkyl or triphenyl(lower)alkyl;  
heterocyclicthio(lower)alkyl,  
in which heterocyclic moiety is  
unsaturated 3 to 8-membered

heteromonocyclic group containing 1 to 4  
nitrogen atom(s);

lower alkenyl; carboxy(lower)alkenyl;  
lower alkoxycarbonyl(lower)alkenyl; lower  
alkynyl; cyclo(lower)alkenyl; or lower  
alkanoyl],

lower alkylidene, or oxo,

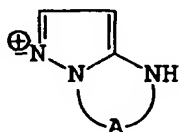
R<sup>4</sup> is a group of the formula :



[wherein R<sup>7</sup> is hydroxy(lower)alkyl, lower  
alkanoyloxy(lower)alkyl,  
carbamoyloxy(lower)alkyl,

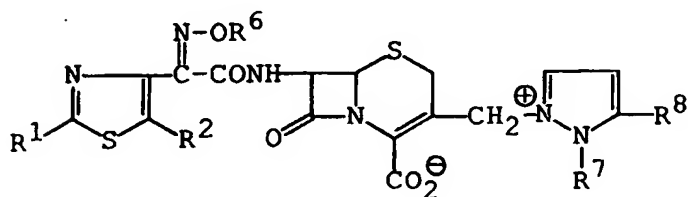
R<sup>8</sup> is amino or lower alkanoylamino, and  
R<sup>9</sup> is hydrogen],

or a group of the formula :



(wherein A is lower alkylene).

4. A compound of claim 3, which is  
a compound of the formula :



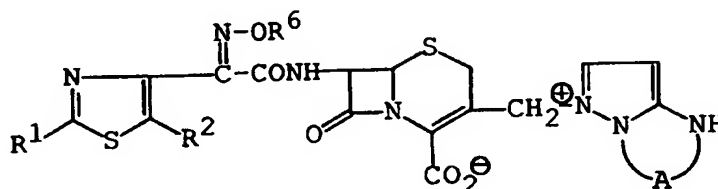
wherein  $R^1$  is amino,  
 $R^2$  is as defined above,  
 $R^6$  is as defined above,  
 $R^7$  is hydroxy(lower)alkyl, and  
 $R^8$  is amino.

5. A compound of claim 4, wherein  
 $R^2$  is halogen, and  
 $R^6$  is halo(lower)alkyl or cyano(lower)alkyl.

6. A compound of claim 5, which is  
 $7\beta$ -[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-(2-fluoroethoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

7. A compound of claim 5, which is  
 $7\beta$ -[(Z)-2-(2-amino-5-chlorothiazol-4-yl)-2-cyanomethoxyiminoacetamido]-3-[5-amino-1-(2-hydroxyethyl)-2-pyrazolio]methyl-3-cephem-4-carboxylate.

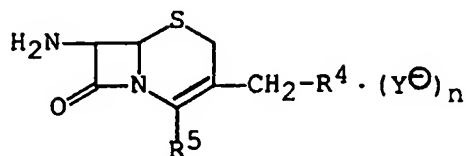
8. A compound of claim 3, which is a compound of the formula :



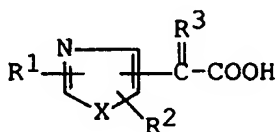
wherein  $R^1$  is amino,  
 $R^2$  is halogen,  
 $R^6$  is hydrogen, lower alkyl,  
halo(lower)alkyl, cyano(lower)alkyl, or  
lower alkanoyl, and  
A is lower alkylene.

9. A process for the preparation of a cephem compound of claim 1 or a salt thereof, which comprises

1) reacting a compound of the formula :

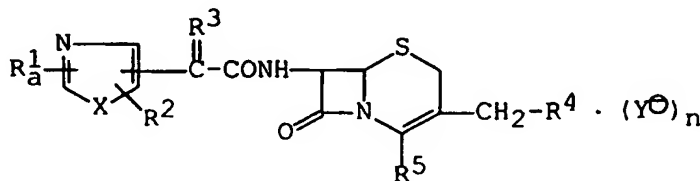


or its reactive derivative at the amino group,  
or a salt thereof, with a compound of the formula :

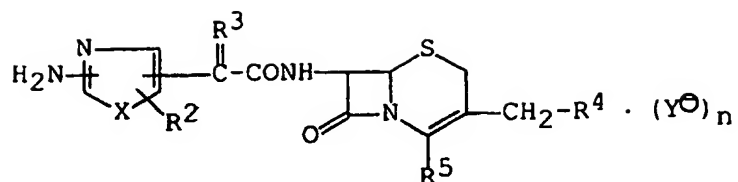


or its reactive derivative at the carboxy group,  
or a salt thereof, or

2) subjecting a compound of the formula :



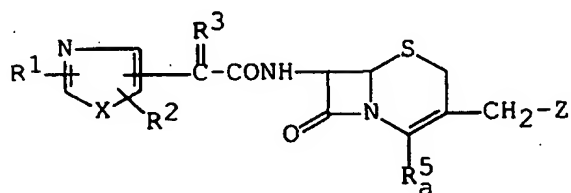
or a salt thereof, to elimination reaction of the amino  
protective group in  $R_a^1$ , to give a compound of the  
formula :



5

or a salt thereof, or

10 3) reacting a compound of the formula :



15

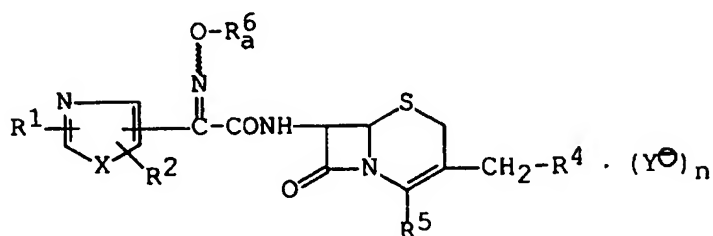
or a salt thereof, with a compound of the formula :



20

or a salt thereof, or

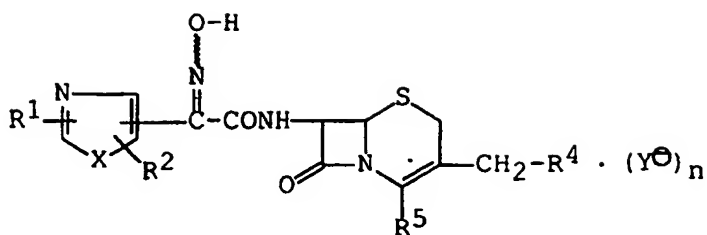
4) subjecting a compound of the formula :



30

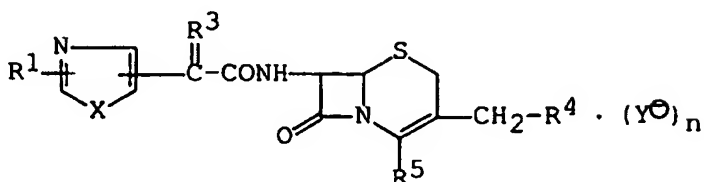
or a salt thereof, to elimination of hydroxy protective group, to give a compound of the formula :

35

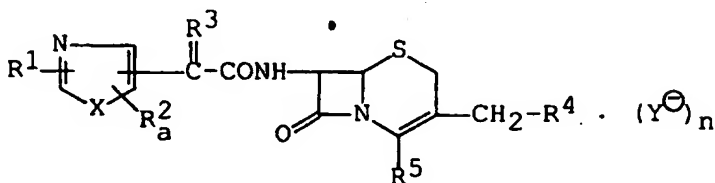


or a salt thereof, or

5) subjecting a compound of the formula :



or a salt thereof, to introduction reaction of halogen,  
to give a compound of the formula :



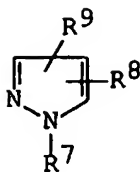
or a salt thereof,

wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{X}$ ,  $\text{Y}^\ominus$  and  $n$  are each as  
defined in claim 1,

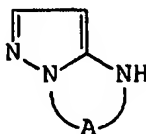
$\text{R}_a^1$  is a protected amino,

$\text{R}_a^2$  is halogen,

$\text{R}_a^4$  is a compound of the formula :



(wherein  $R^7$ ,  $R^8$  and  $R^9$  are each  
as defined above)  
or a compound of the formula :



(wherein A is as defined above),

$R_{a}^5$  is carboxy or a protected carboxy,

$R_{a}^6$  is cyclo(lower)alkenyl or acyl,

Z is a leaving group.

10. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

11. A method for the treatment of infectious diseases which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

12. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an antimicrobial agent.

13. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for the preparation of a medicament.



## INTERNATIONAL SEARCH REPORT

International Appl. No.

PCT/JP 97/01416

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D501/46 A61K31/545

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 427 248 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 15 May 1991 see claims 1-11 ---	1-13
X	EP 0 332 156 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 13 September 1989 see claims 1-14 ---	1-13
Y	EP 0 149 487 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 24 July 1985 see claims 1-9 ---	1-13
Y	EP 0 287 116 A (EISAI CO., LTD.) 19 October 1988 see claims 1-7; examples 9,10 ---	1-13
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

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Date of the actual completion of the international search

11 September 1997

Date of mailing of the international search report

02.10.97

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## INTERNATIONAL SEARCH REPORT

International Appl. No.

PCT/JP 97/01416

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 223 246 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 27 May 1987 see claims 1-16 ---	1-13
Y	WO 92 00981 A (DAE WOONG PHARMACEUTICAL CO., LTD.) 23 January 1992 see claims 1-17 ---	1-13
Y	DATABASE WPI Week 9211 Derwent Publications Ltd., London, GB; AN 92-084412 XP002040499 & JP 04 026 692 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 29 January 1992 see abstract -----	1-13

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 97/01416

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 427248 A	15-05-91	CA 2029638 A JP 3163087 A US 5302712 A US 5215982 A	11-05-91 15-07-91 12-04-94 01-06-93
EP 332156 A	13-09-89	AT 146476 T AU 3101789 A CN 1036959 A DE 68927554 D DK 113289 A JP 2015091 A OA 9239 A PH 25911 A PT 89935 B SU 1804462 A US 5173485 A US 5366970 A	15-01-97 14-09-89 08-11-89 30-01-97 10-09-89 18-01-90 30-06-92 19-12-91 31-05-94 23-03-93 22-12-92 22-11-94
EP 149487 A	24-07-85	JP 1875777 C JP 6000789 B JP 60155183 A US 4590186 A	07-10-94 05-01-94 15-08-85 20-05-86
EP 287116 A	19-10-88	AT 119907 T CA 1297097 A DE 3853311 D DE 3853311 T ES 2068813 T JP 1025784 A JP 2571815 B US 4929612 A	15-04-95 10-03-92 20-04-95 07-09-95 01-05-95 27-01-89 16-01-97 29-05-90
EP 223246 A	27-05-87	AU 6556186 A DE 3689684 D DE 3689684 T JP 7116201 B JP 62174085 A KR 9400111 B OA 8444 A US 5194432 A	28-05-87 07-04-94 23-06-94 13-12-95 30-07-87 05-01-94 30-06-88 16-03-93

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/JP 97/01416

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 223246 A		US 4960766 A	02-10-90
WO 9200981 A	23-01-92	KR 9400112 B	05-01-94
		JP 7033389 B	12-04-95
		JP 5502884 T	20-05-93
		US 5336673 A	09-08-94